# Kongeriget Danmark

Patent application No.:     PA 2002 00763

Date of filing:     17. May 2002

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Title: Diamino-functional chalcones.

IPC: -

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**Patent- og Varemærkestyrelsen**
Økonomi- og Erhvervsministeriet

18. June 2003

John Nielsen

**PATENT- OG VAREMÆRKESTYRELSEN**

# DIAMINO-FUNCTIONAL CHALCONES

## FIELD OF THE INVENTION

The present invention relates to a novel class of chalcone derivatives and analogues and to their use as pharmaceutically active agents, in particular against bacterial and parasitic
5  infections

Furthermore, the invention relates to a method of predicting whether a chemical compound has a potential inhibitory effect against an organism selected from *Helicobacter pylori* and *Plasmodium falciparum* The prediction is based on the ability of the chemical
10  compound to act as an inhibitior of the enzyme dihydroorotate dehydrogenase which is involved in the synthesis of pyrimidine in prokaryotic as well as eukaryotic cells such as bacteria, parasites, fungi, helminths and any type of mammalian cells such as human cells

## BACKGROUND OF THE INVENTION

Chalcones, e g , for use against parasitic infections are known from earlier patent
15  applications assigned to the applicant, e g  WO 93/17671 and WO 99/00114

The bioavailability for several of the known chalcones is low due to the low solubility of the compounds  The compounds do not typically dissolve in the intestine and are therefore not available for absorption
20
The spread of antimicrobial resistance determinants particular among nosocomial bacterial pathogens is an increasing problem  Such resistant pathogens include *Staphylococcus aureus* resistant to methicillin and thus to all β-lactam-antibiotics and Enterococci resistant to vancomycin (VRE)  Such resistant bacteria pose a significant therapeutic challenge and
25  bacterial strains resistant to all currently available antimicrobials are emerging Furthermore, bacterial species intrinsically resistant to commonly employed antimicrobials are being recognized as important opportunistic pathogens in the setting of long-term immunocompromized patients An example of this is *Stenotrophomonas maltophilia* which possesses a β-lactamase rendering the bacteria intrinsically resistant to carbapenems  As
30  cross-resistance within a given class of antibiotics often occurs the development of new classes of antibiotics is a neccisity to counter the emerging threat of bacterial resistance

Thus, there is a need for improved chalcone derivatives for therapeutic or prophylactic use against parasites and bacteria

35  **BRIEF DESCRIPTION OF THE FIGURES**

Figure 1 illustrates the general synthetic scheme for the preparation of diamino-functional chalcones where the aromatic rings are phenyl rings  $R^4$= H (yielding the B ring) or $CH_3$ (yielding the A ring), $R^1$, $R^2$, $R^3$ and Z are as defined herein

Figure 2 illustrates the scheme for the preparation of diamino (aminoacylamino)-functional chalcones where the aromatic rings are phenyl $R^1$, $R^2$ and $R^3$ are as defined herein, $R_4=$ H or $CH_3$, and $Y=(C(R^H)_2)_{n\,1}$

5  Figure 3 illustrates the synthesis of diamino-dihydrochalcones $R^1$, $R^2$, $R^3$ and Z are as defined herein

Figure 4 illustrates a time-kill curve of I-031 against S aureus ATCC29213 Bacterial growth is inhibited at concentrations at or above the MIC (MIC=37 5 µM) As CFU counts
10  per ml decreases at concentrations of compound above the MIC, the compound is bactericidal The reduction in CFU/ml is faster as the concentration of test compound increases above the MIC This indicates that the bactericidal action of the compound is primarily dependent on the concentration of the test compound

15  Figure 5 illustrates a time-kill curve of I-070 against S aureus ATCC29213 Bacterial growth is inhibited at concentrations of test compound at or above the MIC (MIC=9 4 µM) As CFU counts per ml decreases at concentrations of compound above the MIC, the compound is bactericidal The rate of reduction of CFU/ml is not significantly affected by increasing concentrations of test compound Thus, the bactericidal action of the compound
20  is primarily dependent on incubation time

Figure 6 illustrates a dose-respons curve of LicA and one of the novel diamino-chalcones (I-103) at *Plasmodium falciparum* As shown at the figure, I-103 is 10 times more potent than LicA
25

DESCRIPTION OF THE INVENTION

The present inventors have found that the diamino-functional chalcone defined herein exhibit interesting biological properties combined with improved metabolic and
30  physicochemical properties which make the compound useful as drug substances, in particular as antiparasitic agents, bacteriostatic agents, and bacteriocidal agents

It is believed that the diamino group or groups of the diamino-functional chalcone will be charged according to pH of the medium and the pKa of the compound The solubility of the
35  charged compounds is many times higher than the solubility of the neutral compounds As the diamino-functional chalcones will be partially charged (i e soluble) at the pH in the intestine, they will dissolve in the gastric juices and be available for absorption The bioavailability of the diamino-functional chalcones will therefore be improved many times compared to the known neutral chalcones making the compounds generally useful as drug
40  candidates Also, the diamino-functional chalcones have different pKa values which enable the selection of a chalcone derivative with optimal *charged/non-charged* ratio at a given pH value

3

The usefulness of the known chalcones as drug candidates have been limited by the metabolism of the compounds resulting in short half-lives *in vivo* The inventors have now found that introduction of a diamino group in the chalcone derivative changes the metabolic properties and the compounds prepared show improved metabolic stability

5    Futhermore, the inventors have found that the diamino-functional chalcones defined herein exhibit excellent bacteriocidal and bacteriostatic properties, even against multi-resistant bacteria strains

10  Thus, the present invention provides chalcone derivatives and analogues as defined in claim 1, i e a compound of the general formula

$$Y^1(X^1)-Ar^1-C(=O)-V-Ar^2(X^2)Y^2$$
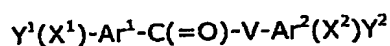
15  wherein $Ar^1$ and $Ar^2$ independently are selected from aromatic rings (aryl) and heteroaromatic rings (heteroaryl),

V designates $-CH_2-CH_2-$, $-CH=CH-$ or $-C{\equiv}C-$, preferably $-CH=CH-$,

20  one or both of $Y^1$ and $Y^2$ independently represent at least one, such as 1-2, e g one, diamino-functional substituent(s) of the formula

$$-NR^3-Z-N(R^1)R^2$$
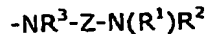
25  wherein Z is a biradical $-(C(R^H)_2)_n-$, wherein n is an integer in the range of 1-6, preferably 2-4, such as 2-3, and each $R^H$ is independently selected from hydrogen and $C_{1\,6}$-alkyl, or two $R^H$ on the same carbon atom may designate =O,

R$^1$ and R$^2$ independently are selected from hydrogen, optionally substituted $C_{1\,12}$-alkyl,
30  optionally substituted $C_{2\,12}$-alkenyl, optionally substituted $C_{4\,12}$-alkadienyl, optionally substituted $C_{6\,12}$-alkatrienyl, optionally substituted $C_{2\,12}$-alkynyl, optionally substituted $C_{1\,12}$-alkoxycarbonyl, optionally substituted $C_{1-12}$-alkylcarbonyl, optionally substituted aryl, optionally substituted aryloxycarbonyl, optionally substituted arylcarbonyl, optionally substituted heteroaryl, optionally substituted heteroaryloxycarbonyl, optionally substituted
35  heteroarylcarbonyl, aminocarbonyl, mono- and di($C_{1-6}$-alkyl)aminocarbonyl, amino-$C_{1\,6}$-alkyl-aminocarbonyl, mono- and di($C_{1-6}$-alkyl)amino-$C_{1\,6}$-alkyl-aminocarbonyl, or $R^1$ and $R^2$ together with the nitrogen atom to which they are attached ($-N(R^1)R^2$) form an optionally substituted nitrogen-containing heterocyclic ring,
R$^3$ is selected from hydrogen, $C_{1\,6}$-alkyl, and $C_{1\,6}$-alkylcarbonyl, said alkyl and alkylcarbonyl
40  optionally carrying substituent(s) selected from halogen, hydroxy, $C_{1\,6}$-alkoxy, carboxy, $C_{1\,6}$-alkoxycarbonyl, $C_{1\,6}$-alkylcarbonyl, amino, mono- and di($C_{1\,6}$-alkyl)amino, and aryl optionally substituted 1-3 times with $C_{1\,4}$-alkyl, $C_{1\,4}$-alkoxy, nitro, cyano, amino or halogen, or $R^1$ and $R^3$ together form a biradical $Z^*$ which is as defined for Z,

$X^1$ and $X^2$ independently designates 0-5, preferably 0-4, such as 0-3, e g 0-2, substituents, where such optional substituents independently are selected from optionally substituted $C_{1\ 12}$-alkyl, optionally substituted $C_{2\ 12}$-alkenyl, optionally substituted $C_{4\ 12}$-alkadienyl, optionally substituted $C_{6\ 12}$-alkatrienyl, optionally substituted $C_{2\ 12}$-alkynyl, hydroxy, optionally substituted $C_{1-12}$-alkoxy, optionally substituted $C_{2\ 12}$-alkenyloxy, carboxy, optionally substituted $C_{1-12}$-alkoxycarbonyl, optionally substituted $C_{1\ 12}$-alkylcarbonyl, formyl, $C_{1\ 6}$-alkylsulphonylamino, optionally substituted aryl, optionally substituted aryloxycarbonyl, optionally substituted aryloxy, optionally substituted arylcarbonyl, optionally substituted arylamino, arylsulphonylamino, optionally substituted heteroaryl, optionally substituted heteroaryloxycarbonyl, optionally substituted heteroaryloxy, optionally substituted heteroarylcarbonyl, optionally substituted heteroarylamino, heteroarylsulphonylamino, optionally substituted heterocyclyl, optionally substituted heterocyclyloxycarbonyl, optionally substituted heterocyclyloxy, optionally substituted heterocyclylcarbonyl, optionally substituted heterocyclylamino, heterocyclylsulphonylamino, amino, mono- and di($C_{1\ 6}$-alkyl)amino, carbamoyl, mono- and di($C_{1\ 6}$-alkyl)aminocarbonyl, amino-$C_{1\ 6}$-alkyl-aminocarbonyl, mono- and di($C_{1\ 6}$-alkyl)amino-$C_{1\ 6}$-alkyl-aminocarbonyl, $C_{1-6}$-alkylcarbonylamino, amino-$C_{1\ 6}$-alkyl-carbonylamino, mono- and di($C_{1\ 6}$-alkyl)amino-$C_{1\ 6}$-alkyl-carbonylamino, cyano, guanidino, carbamido, $C_{1\ 6}$-alkanoyloxy, $C_{1\ 6}$-alkylsulphonyl, $C_{1\ 6}$-alkylsulphinyl, $C_{1-6}$-alkylsulphonyl-oxy, aminosulfonyl, mono- and di($C_{1\ 6}$-alkyl)aminosulfonyl, nitro, optionally substituted $C_{1\ 6}$-alkylthio, and halogen, where any nitrogen-bound $C_{1-6}$-alkyl may be substituted with hydroxy, $C_{1\ 6}$-alkoxy, $C_{2\ 6}$-alkenyloxy, amino, mono- and di($C_{1\ 6}$-alkyl)amino, carboxy, $C_{1\ 6}$-alkylcarbonylamino, halogen, $C_{1\ 6}$-alkylthio, $C_{1\ 6}$-alkyl-sulphonyl-amino, or guanidine,

and salts thereof

The substituents $R^1$ and $R^2$ carried by the one nitrogen atom of the diamino substituent, and $R^3$ carried by the other nitrogen atom of the diamino substituent are believed to slightly alter the pKa value of the chalcone derivative Thus, the particular selection of the groups $R^1$, $R^2$ and $R^3$ can be used to "fine-tune" the pKa value in view of the particular condition or disease and the intended route of administration

In one embodiment, $R^1$ and $R^2$ are independently selected from hydrogen, optionally substituted $C_{1-12}$-alkyl, optionally substituted $C_{2\ 12}$-alkenyl, optionally substituted $C_{2\ 12}$-alkynyl, optionally substituted $C_{1-12}$-alkylcarbonyl, arylcarbonyl, heteroarylcarbonyl, aminocarbonyl, mono- and di($C_{1\ 6}$-alkyl)aminocarbonyl, amino-$C_{1\ 6}$-alkyl-aminocarbonyl, and mono- and di($C_{1\ 6}$-alkyl)amino-$C_{1\ 6}$-alkyl-aminocarbonyl In particular $R^1$ and $R^2$ are independently selected from hydrogen, optionally substituted $C_{1-6}$-alkyl, optionally substituted $C_{1\ 6}$-alkylcarbonyl, heteroarylcarbonyl, aminocarbonyl, mono- and di($C_{1\ 6}$-alkyl)aminocarbonyl, amino-$C_{1\ 6}$-alkyl-aminocarbonyl, mono- and di($C_{1\ 6}$-alkyl)amino-$C_{1\ 6}$-alkyl-aminocarbonyl

In another embodiment, $R^1$ and $R^2$ together with the nitrogen atom to which they are attached (-N($R^1$)$R^2$) form an optionally substituted nitrogen-containing heterocyclic ring

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In a further embodiment, $R^3$ is selected from hydrogen and methyl, in particular methyl

The selection of the substituents $X^1$ and $X^2$ is not very critical  Thus, it is believed that
5  these substituents can be chosen fairly freely

However, in still a further embodiment, $X^1$ and $X^2$ independently designates 0-4, such as 0-
3, e g  0-2, substituents, where such optional substituents independently are selected from
optionally substituted $C_{1\text{-}12}$-alkyl, hydroxy, optionally substituted $C_{1\text{-}12}$-alkoxy, optionally
10  substituted $C_{2\text{-}12}$-alkenyloxy, carboxy, optionally substituted $C_{1\text{-}12}$-alkylcarbonyl, formyl,
$C_{1\text{-}6}$-alkylsulphonylamino, optionally substituted aryl, optionally substituted aryloxy-
carbonyl, optionally substituted aryloxy, optionally substituted arylcarbonyl, optionally
substituted arylamino, arylsulphonylamino, optionally substituted heteroaryl, optionally
substituted heteroarylamino, optionally substituted heteroarylcarbonyl, optionally
15  substituted heteroaryloxy, heteroarylsulphonylamino, optionally substituted heterocyclyl,
optionally substituted heterocyclyloxy, optionally substituted heterocyclylamino, amino,
mono- and di($C_{1\text{-}6}$-alkyl)amino, carbamoyl, mono- and di($C_{1\text{-}6}$-alkyl)aminocarbonyl, amino-
$C_{1\text{-}6}$-alkyl-aminocarbonyl, mono- and di($C_{1\text{-}6}$-alkyl)amino-$C_{1\text{-}6}$-alkyl-aminocarbonyl, $C_{1\text{-}6}$-
alkylcarbonylamino, amino-$C_{1\text{-}6}$-alkyl-carbonylamino, mono- and di($C_{1\text{-}6}$-alkyl)amino-$C_{1\text{-}6}$-
20  alkyl-carbonylamino, guanidino, carbamido, $C_{1\text{-}6}$-alkylsulphonyl, $C_{1\text{-}6}$-alkylsulphinyl, $C_{1\text{-}6}$-
alkylsulphonyloxy, optionally substituted $C_{1\text{-}6}$-alkylthio, aminosulfonyl, mono- and di($C_{1\text{-}6}$-
alkyl)aminosulfonyl, and halogen, where any nitrogen-bound $C_{1\text{-}6}$-alkyl may be substituted
with hydroxy, $C_{1\text{-}6}$-alkoxy, and/or halogen, in particular $X^1$ and $X^2$ independently designates
0-3, e g  0-2, substituents, where such optional substituents independently are selected
25  from optionally substituted $C_{1\text{-}6}$-alkyl, hydroxy, optionally substituted $C_{1\text{-}6}$-alkoxy, carboxy,
optionally substituted $C_{1\text{-}6}$-alkylcarbonyl, $C_{1\text{-}6}$-alkylsulphonylamino, optionally substituted
aryl, optionally substituted aryloxy, optionally substituted arylamino, arylsulphonylamino,
optionally substituted heteroaryl, optionally substituted heteroarylamino, heteroaryl-
sulphonylamino, amino, mono- and di($C_{1\text{-}6}$-alkyl)amino, carbamoyl, $C_{1\text{-}6}$-alkylcarbonylami-
30  no, guanidino, carbamido, optionally substituted $C_{1\text{-}6}$-alkylthio, optionally substituted
heterocyclyl, optionally substituted heterocyclyloxy, optionally substituted heterocyclyl-
amino and halogen, where any nitrogen-bound $C_{1\text{-}6}$-alkyl may be substituted with hydroxy,
$C_{1\text{-}6}$-alkoxy, and/or halogen

35  The group V is relevant with respect to the spatial orientation of the rings $Ar^1$ and $Ar^2$
Thus, the group V may be $-CH_2-CH_2-$, $-CH=CH-$ or $-C\equiv C-$  Preliminary results have showns
that the embodiments wherein V designates $-CH=CH-$ yields valuable chalcone derivatives

The expression "chalcone derivative" has been assigned to the compounds of the above
40  formula in that the overall structure namely $Ar^1-C(=O)-C-C-Ar^2$ resembles that of the
chalcone structure  This being said, $Ar^1$ and $Ar^2$ are selected from aromatic rings and
heteroaromatic rings  It is currently believed that particularly interesting compounds are
those where at least one of $Ar^1$ and $Ar^2$, preferably both, are aromatic rings, in particular
phenyl rings  This being said, the inventors envisage that the functionality of the

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compounds may be substantially preserved (or even improved) when one or both of $Ar^1$ and $Ar^2$ are heteroaromatic rings

In one embodiment, at least one or $Ar^1$ and $Ar^2$ is selected from thiazolyl, pyrrolyl, 5 imidazolyl, pyrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, thiophenyl, quinolyl, isoquinolyl, and indolyl

In another embodiment, both of $Ar^1$ and $Ar^2$ are phenyl rings and $Y^1$ represent at least one diamino-functional substituent

10

In a further embodiment, $X^2$ represents at least one substituent selected from $C_{1-6}$-alkyl, $C_{1-6}$-alkoxy, $C_{1-6}$-alkylcarbonyl, optionally substituted aryl, optionally substituted aryloxy, optionally substituted arylamino, optionally substituted heteroaryl, optionally substituted heteroarylamino, mono- and di($C_{1-6}$-alkyl)amino, $C_{1-6}$-alkylcarbonylamino, optionally 15 substituted $C_{1-6}$-alkylthio, optionally substituted heterocyclyl, optionally substituted heterocyclyloxy, optionally substituted heterocyclylamino and halogen, in particular, $X^2$ represents at least two halogen atoms

The Z group represents the biradical between the two nitrogen atoms of the diamino 20 functionality This group Z is typically a biradical $-(C(R^H)_2)_n-$, wherein n is an integer in the range of 1-6, preferably 2-4, such as 2-3, where each $R^H$ is independently selected from hydrogen and $C_{1-6}$-alkyl, or two $R^H$ on the same carbon atom may designate =O A particular example of Z is $-(CH_2)_n-$ wherein n is 2-4, such as 2-3

25 Thus, in a particular embodiment, one of $Y^1$ and $Y^2$ represent a substituent of the formula
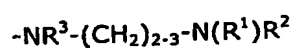
$-NR^3-(CH_2)_{2-3}-N(R^1)R^2$

wherein $R^3$ is selected from hydrogen and methyl, $R^1$ and $R^2$ is selected from hydrogen and 30 $C_{1-6}$-alkyl Furthermore, V is preferably -CH=CH-, and $Ar^1$ and $Ar^2$ both are phenyl rings

In a further embodiment, one of $Y^1$ and $Y^2$ represents a substituent of the formula

$-NR^3-C(=O)-(CH_2)_{1-4}-N(R^1)R^2$
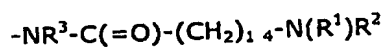
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wherein $R^3$ is selected from hydrogen and methyl, $R^1$ and $R^2$ is selected from hydrogen and $C_{1-6}$-alkyl Furthermore, V is preferably -CH=CH-, and $Ar^1$ and $Ar^2$ both are phenyl rings

Definitions

40

In the present context, the term "bacteriostatic" is intended to describe an antimicrobial activity of a test compund, characterized by an inhibition of bacterial growth in the absence of a reduction of viable bacteria (bacterial kill) during incubation with the test

compound, as evidenced in the killing curve determination by a stationary number of colony forming units (CFU) during incubation time

In the present context, the term "bacteriocidal" is intended to describe an antimicrobial
5  activity of a test compound, characterized by the reduction of viable bacteria (bacterial kill) during incubation with the test compound, as evidenced in the killing curve determination by a reduction of colony forming units (CFU) during incubation time

In the present contest, the term "antiparasitic" is intended to describe the ability of a test
10 compound to upon incubation in vitro with a culture of parasites, e g *Leishmania major* or *Plasmodium falciparum*, to inhibit metabolic labelling of the parasites by at least 50% compared to mock treated control cultures

In the present context, the term "$C_{1-12}$-alkyl" is intended to mean a linear, cyclic or
15 branched hydrocarbon group having 1 to 12 carbon atoms, such as methyl, ethyl, propyl, *iso*-propyl, cyclopropyl, butyl, *tert*-butyl, *iso*-butyl, cyclobutyl, pentyl, cyclopentyl, hexyl, cyclohexyl, etc Analogously, the term "$C_{1-6}$-alkyl" is intended to mean a linear, cyclic or branched hydrocarbon group having 1 to 6 carbon atoms, such as methyl, ethyl, propyl, *iso*-propyl, pentyl, cyclopentyl, hexyl, cyclohexyl, and the term "$C_{1-4}$-alkyl" is intended to
20 cover linear, cyclic or branched hydrocarbon groups having 1 to 4 carbon atoms, e g methyl, ethyl, propyl, *iso* propyl, cyclopropyl, butyl, *iso*-butyl, *tert*-butyl, cyclobutyl

Whenever the term "$C_{1-12}$-alkyl" is used herein, it should be understood that a particularly interesting embodiment thereof is "$C_{1-6}$-alkyl"
25
Similarly, the terms "$C_{2-12}$-alkenyl", "$C_{4-12}$-alkadienyl", and "$C_{6-12}$-alkatrienyl" are intended to cover linear, cyclic or branched hydrocarbon groups having 2 to 12, 4 to 12, and 6 to 12, carbon atoms, respectively, and comprising one, two, and three unsaturated bonds, respectively Examples of alkenyl groups are vinyl, allyl, butenyl, pentenyl, hexenyl,
30 heptenyl, octenyl, heptadecaenyl Examples of alkadienyl groups are butadienyl, pentadienyl, hexadienyl, heptadienyl, heptadecadienyl Examples of alkatrienyl groups are hexatrienyl, heptatrienyl, octatrienyl, and heptadecatrienyl Preferred examples of alkenyl are vinyl, allyl, butenyl, especially allyl

35 Similarly, the term "$C_{2-12}$-alkynyl" is intended to mean a linear or branched hydrocarbon group having 2 to 12 carbon atoms and comprising a triple bond Examples hereof are ethynyl, propynyl, butynyl, octynyl, and dodecaynyl

Whenever the terms "$C_{2-12}$-alkenyl", "$C_{4-12}$-alkadienyl", "$C_{6-12}$-alkatrienyl", and "$C_{2-12}$-
40 alkynyl" are used herein, it should be understood that a particularly interesting embodiment thereof are the variants having up to six carbon atoms

In the present context, i e in connection with the terms "alkyl", "alkenyl", "alkadienyl", "alkatrienyl", and "alkynyl", the term "optionally substituted" is intended to mean that the

group in question may be substituted one or several times, preferably 1-3 times, with group(s) selected from hydroxy (which when bound to an unsaturated carbon atom may be present in the tautomeric keto form), $C_{1-6}$-alkoxy (i e $C_{1-6}$-alkyl-oxy), $C_{2-6}$-alkenyloxy, carboxy, oxo (forming a keto or aldehyde functionality), $C_{1-6}$-alkoxycarbonyl, $C_{1-6}$-
5 alkylcarbonyl, formyl, aryl, aryloxycarbonyl, aryloxy, arylamino, arylcarbonyl, heteroaryl, heteroarylamino, heteroaryloxycarbonyl, heteroaryloxy, heteroarylcarbonyl, amino, mono- and di($C_{1-6}$-alkyl)amino, carbamoyl, mono- and di($C_{1-6}$-alkyl)aminocarbonyl, amino-$C_{1-6}$-alkyl-aminocarbonyl, mono- and di($C_{1-6}$-alkyl)amino-$C_{1-6}$-alkyl-aminocarbonyl, $C_{1-6}$-alkyl-carbonylamino, cyano, guanidino, carbamido, $C_{1-6}$-alkyl-sulphonyl-amino, aryl-sulphonyl-
10 amino, heteroaryl-sulphonyl-amino, $C_{1-6}$-alkanoyloxy, $C_{1-6}$-alkyl-sulphonyl, $C_{1-6}$-alkyl-sulphinyl, $C_{1-6}$-alkylsulphonyloxy, nitro, $C_{1-6}$-alkylthio, halogen, where any aryl and heteroaryl may be substituted as specifically describe below for "optionally substituted aryl and heteroaryl", and any alkyl, alkoxy, and the like representing substituents may be substituted with hydroxy, $C_{1-6}$-alkoxy, $C_{2-6}$-alkenyloxy, amino, mono- and di($C_{1-6}$-
15 alkyl)amino, carboxy, $C_{1-6}$-alkylcarbonylamino, halogen, $C_{1-6}$-alkylthio, $C_{1-6}$-alkyl-sulphonyl-amino, or guanidine

Preferably, the substituents are selected from hydroxy (which when bound to an unsaturated carbon atom may be present in the tautomeric keto form), $C_{1-6}$-alkoxy (i e
20 $C_{1-6}$-alkyl-oxy), $C_{2-6}$-alkenyloxy, carboxy, oxo (forming a keto or aldehyde functionality), $C_{1-6}$-alkylcarbonyl, formyl, aryl, aryloxy, arylamino, arylcarbonyl, heteroaryl, heteroarylamino, heteroaryloxy, heteroarylcarbonyl, amino, mono- and di($C_{1-6}$-alkyl)amino, carbamoyl, mono- and di($C_{1-6}$-alkyl)aminocarbonyl, amino-$C_{1-6}$-alkyl-aminocarbonyl, mono- and di($C_{1-6}$-alkyl)amino-$C_{1-6}$-alkyl-aminocarbonyl, $C_{1-6}$-alkylcarbony-
25 lamino, guanidino, carbamido, $C_{1-6}$-alkyl-sulphonyl-amino, $C_{1-6}$-alkyl-sulphonyl, $C_{1-6}$-alkyl-sulphinyl, $C_{1-6}$-alkylthio, halogen, where any aryl and heteroaryl may be substituted as specifically describe below for "optionally substituted aryl and heteroaryl"

Especially preferred examples are hydroxy, $C_{1-6}$-alkoxy, $C_{2-6}$-alkenyloxy, amino, mono- and
30 di($C_{1-6}$-alkyl)amino, carboxy, $C_{1-6}$-alkylcarbonylamino, halogen, $C_{1-6}$-alkylthio, $C_{1-6}$-alkyl-sulphonyl-amino, and guanidine

"Halogen" includes fluoro, chloro, bromo, and iodo

35 In the present context the term "aryl" is intended to mean a fully or partially aromatic carbocyclic ring or ring system, such as phenyl, naphthyl, 1,2,3,4-tetrahydronaphthyl, anthracyl, phenanthracyl, pyrenyl, benzopyrenyl, fluorenyl and xanthenyl, among which phenyl is a preferred example

40 The term "heteroaryl" is intended to mean a fully or partially aromatic carbocyclic ring or ring system where one or more of the carbon atoms have been replaced with heteroatoms, e g nitrogen (=N- or -NH-), sulphur, and/or oxygen atoms Examples of such heteroaryl groups are oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrrolyl, imidazolyl, pyrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, triazinyl, coumaryl, furyl, thiophenyl, quinolyl,

benzothiazolyl, benzotriazolyl, benzodiazolyl, benzooxozolyl, phthalazinyl, phthalanyl, triazolyl, tetrazolyl, isoquinolyl, acridinyl, carbazolyl, dibenzazepinyl, indolyl, benzopyrazolyl, phenoxazonyl Particularly interesting heteroaryl groups are oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrrolyl, imidazolyl, pyrazolyl, pyridinyl, pyrimidinyl,
5  pyrazinyl, pyridazinyl, furyl, thiophenyl, quinolyl, triazolyl, tetrazolyl, isoquinolyl, indolyl in particular pyrrolyl, imidazolyl, pyridinyl, pyrimidinyl, thiophenyl, quinolyl, tetrazolyl, and isoquinolyl

The term "heterocyclyl" is intended to mean a non-aromatic carbocyclic ring or ring system
10  where one or more of the carbon atoms have been replaced with heteroatoms, e g nitrogen (=N- or -NH-), sulphur, and/or oxygen atoms Examples of such heterocyclyl groups are imidazolidine, piperazine, hexahydropyridazine, hexahydropyrimidine, diazepane, diazocane, pyrrolidine, piperidine, azepane, azocane, aziridine, azirine, azetidine, pyroline, tropane, oxazinane (morpholine), azepine, dihydroazepine,
15  tetrahydroazepine, and hexahydroazepine, oxazolane, oxazepane, oxazocane, thiazolane, thiazinane, thiazepane, thiazocane, oxazetane, diazetane, thiazetane, tetrahydrofuran, tetrahydropyran, oxepane, tetrahydrothiophene, tetrahydrothiopyrane, thiepane, dithiane, dithiepane, dioxane, dioxepane, oxathiane, oxathiepane The most interesting examples are imidazolidine, piperazine, hexahydropyridazine, hexahydropyrimidine, diazepane,
20  diazocane, pyrrolidine, piperidine, azepane, azocane, azetidine, tropane, oxazinane (morpholine), oxazolane, oxazepane, thiazolane, thiazinane, and thiazepane, in particular imidazolidine, piperazine, hexahydropyridazine, hexahydropyrimidine, diazepane, pyrrolidine, piperidine, azepane, oxazinane (morpholine), and thiazinane

25  In the present context, i e in connection with the terms "aryl", "heteroaryl", and heterocyclyl, the term "optionally substituted" is intended to mean that the group in question may be substituted one or several times, preferably 1-5 times, in particular 1-3 times) with group(s) selected from hydroxy (which when present in an enol system may be represented in the tautomeric keto form), $C_{1\text{-}6}$-alkyl, $C_{1\text{-}6}$-alkoxy, $C_{2\text{-}6}$-alkenyloxy, oxo
30  (which may be represented in the tautomeric enol form), carboxy, $C_{1\text{-}6}$-alkoxycarbonyl, $C_{1\text{-}6}$-alkylcarbonyl, formyl, aryl, aryloxy, arylamino, aryloxycarbonyl, arylcarbonyl, heteroaryl, heteroarylamino, amino, mono- and di($C_{1\text{-}6}$-alkyl)amino, carbamoyl, mono- and di($C_{1\text{-}6}$-alkyl)aminocarbonyl, amino-$C_{1\text{-}6}$-alkyl-aminocarbonyl, mono- and di($C_{1\text{-}6}$-alkyl)-amino-$C_{1\text{-}6}$-alkyl-aminocarbonyl, $C_{1\text{-}6}$-alkylcarbonylamino, cyano, guanidino, carbamido,
35  $C_{1\text{-}6}$-alkanoyloxy, $C_{1\text{-}6}$-alkyl-sulphonyl-amino, aryl-sulphonyl-amino, heteroaryl-sulphonyl-amino, $C_{1\text{-}6}$-alkyl-suphonyl, $C_{1\text{-}6}$-alkyl-sulphinyl, $C_{1\text{-}6}$-alkylsulphonyloxy, nitro, sulphanyl, amino, amino-sulfonyl, mono- and di($C_{1\text{-}6}$-alkyl)amino-sulfonyl, dihalogen-$C_{1\text{-}4}$-alkyl, trihalogen-$C_{1\text{-}4}$-alkyl, halogen, where aryl and heteroaryl representing substituents may be substituted 1-3 times with $C_{1\text{-}4}$-alkyl, $C_{1\text{-}4}$-alkoxy, nitro, cyano, amino or halogen, and any
40  alkyl, alkoxy, and the like representing substituents may be substituted with hydroxy, $C_{1\text{-}6}$-alkoxy, $C_{2\text{-}6}$-alkenyloxy, amino, mono- and di($C_{1\text{-}6}$-alkyl)amino, carboxy, $C_{1\text{-}6}$-alkylcarbony-lamino, halogen, $C_{1\text{-}6}$-alkylthio, $C_{1\text{-}6}$-alkyl-sulphonyl-amino, or guanidine

Preferably, the substituents are selected from hydroxy, $C_{1-6}$-alkyl, $C_{1-6}$-alkoxy, oxo (which may be represented in the tautomeric enol form), carboxy, $C_{1-6}$-alkylcarbonyl, formyl, amino, mono- and di($C_{1-6}$-alkyl)amino, carbamoyl, mono- and di($C_{1-6}$-alkyl)aminocarbonyl, amino-$C_{1-6}$-alkyl-aminocarbonyl, $C_{1-6}$-alkylcarbonylamino, guanidino, carbamido, $C_{1-6}$-alkyl-

5 sulphonyl-amino, aryl-sulphonyl-amino, heteroaryl-sulphonyl-amino, $C_{1-6}$-alkyl-suphonyl, $C_{1-6}$-alkyl-sulphinyl, $C_{1-6}$-alkylsulphonyloxy, sulphanyl, amino, amino-sulfonyl, mono- and di($C_{1-6}$-alkyl)amino-sulfonyl or halogen, where any alkyl, alkoxy and the like representing substituents may be substituted with hydroxy, $C_{1-6}$-alkoxy, $C_{2-6}$-alkenyloxy, amino, mono- and di($C_{1-6}$-alkyl)amino, carboxy, $C_{1-6}$-alkylcarbonylamino, halogen, $C_{1-6}$-alkylthio, $C_{1-6}$-

10 alkyl-sulphonyl-amino, or guanidine Especially preferred examples are $C_{1-6}$-alkyl, $C_{1-6}$-alkoxy, amino, mono- and di($C_{1-6}$-alkyl)amino, sulphanyl, carboxy or halogen, where any alkyl, alkoxy and the like representing substituents may be substituted with hydroxy, $C_{1-6}$-alkoxy, $C_{2-6}$-alkenyloxy, amino, mono- and di($C_{1-6}$-alkyl)amino, carboxy, $C_{1-6}$-alkylcarbony-lamino, halogen, $C_{1-6}$-alkylthio, $C_{1-6}$-alkyl-sulphonyl-amino, or guanidine

15

In the present context the term "nitrogen-containing heterocyclic ring" is intended to mean heterocyclic ring or ring system in which at least one nitrogen atom is present Such a nitrogen is, with reference to the formula, carrying the substituents $R_1$ and $R_2$ The heterocyclic ring or ring system is a ring or ring system where one or more of the carbon

20 atoms have been replaced with heteroatoms, e g nitrogen (=N- or –N-), sulphur, and/or oxygen atoms Examples of such rings are aromatic rings such as pyridine, pyridazine, pyrimidine, pyrazine, triazine, thiophene, oxazole, isoxazole, thiazole, isothiazole, pyrrole, imidazole, pyrazole, tetrazole, quinoline, benzothiazole, benzotriazole, benzodiazole, benzoxozole, triazole, isoquinoline, indole, benzopyrazole, thiadiazole, and oxadiazole The

25 most interesting examples of aromatic rings are pyridine, pyridazine, pyrimidine, pyrazine, thiophene, tetrazole, oxazole, isoxazole, thiazole, isothiazole, pyrrole, imidazole, pyrazole, quinoline, triazole, isoquinoline, and indole, in particular pyridine, thiophene, imidazole, quinoline, isoquinoline, indole, and tetrazole

30 Other examples of such rings are non-aromatic rings such as imidazolidine, piperazine, hexahydropyridazine, hexahydropyrimidine, diazepane, diazocane, pyrrolidine, piperidine, azepane, azocane, aziridine, azirine, azetidine, pyroline, tropane, oxazinane (morpholine), azepine, dihydroazepine, tetrahydroazepine, and hexahydroazepine, oxazolane, oxazepane, oxazocane, thiazolane, thiazinane, thiazepane, thiazocane, oxazetane,

35 diazetane, and thiazetane The most interesting examples of non-aromatic rings are imidazolidine, piperazine, hexahydropyridazine, hexahydropyrimidine, diazepane, diazocane, pyrrolidine, piperidine, azepane, azocane, azetidine, tropane, oxazinane (morpholine), oxazolane, oxazepane, thiazolane, thiazinane, and thiazepane, in particular imidazolidine, piperazine, hexahydropyridazine, hexahydropyrimidine, diazepane,

40 pyrrolidine, piperidine, azepane, oxazinane (morpholine), and thiazinane

In the present context, i e in connection with the term "nitrogen-containing heterocyclic ring", the term "optionally substituted" is intended to mean that the group in question may be substituted one or several times, preferably 1-5 times, in particular 1-3 times) with

group(s) selected from the same substituents as defined above for "optionally substituted aryl"

As it will be evident from the formulae defined herein and the definitions associated
5 therewith, there may be one or several asymmetric carbon atoms present in the compounds depending on the nature of the substituents  The compounds are intended to include all stereoisomers arising from the presence of any and all isomers as well as mixtures thereof, including racemic mixtures

10 It should furthermore be understood that the compounds defined herein include possible salts thereof, of which pharmaceutically acceptable salts are of course especially relevant for the therapeutic applications  Salts include acid addition salts and basic salts  Examples of acid addition salts are hydrochloride salts, fumarate, oxalate, etc  Examples of basic salts are salts where the (remaining) counter ion is selected from alkali metals, such as
15 sodium and potassium, alkaline earth metals, such as calcium salts, potassium salts, and ammonium ions ($^+N(R')_4$, where the R"s independently designates optionally substituted $C_{1-6}$-alkyl, optionally substituted $C_{2-6}$-alkenyl, optionally substituted aryl, or optionally substituted heteroaryl)  Pharmaceutically acceptable salts are, e g , those described in Remington's - The Science and Practice of Pharmacy, 20th Ed  Alfonso R Gennaro (Ed ),
20 Lippincott, Williams & Wilkins, ISBN  0683306472, 2000, and in Encyclopedia of Pharmaceutical Technology

Thus, chalcones with diamino groups can be prepared in their salt-forms thereby making the compounds particularly useful for pharmaceutical formulations  The use of appropriate
25 selected salt form can be used to control the dissolution rate in vivo  Furthermore, the different salt forms have different bulk-properties which is of importance for the manufacturing process

Preparation of compounds

30
The diamino-functional chalcones defined herein may be produced by methods known *per se* for the preparation of chalcones or methods which are analogous to such methods  Examples of excellent methods for preparing compounds of the 1,3-bis-aromatic-prop-2-enone or the 1,3-bis-aromatic-prop-2-ynone types are given in the following  Further
35 examples of methods for the preparation of the compound used according to the present invention are described in WO 95/06628 and WO 93/17671 and in the references cited therein

Compounds of the general formula I in which V is -CH=CH- can be prepared by reacting a
40 ketone (an acetophenone in the case where $Ar^1$ is phenyl)

$$Y^1(X^1)\text{-Ar}^1 C(=O)\text{-CH}_3$$
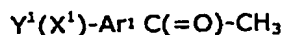
with an aldehyde (a benzaldehyde in the case where $Ar^2$ is phenyl)

$$HCO-Ar^2-(X^2)Y^2$$
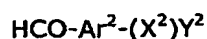
5   wherein $Ar^1$, $Ar^2$, $X^1$, $X^2$, $Y^1$, and $Y^2$ refers to the definitions given elsewhere herein

This reaction, which is a condensation reaction, is suitably carried out under acid or base
catalysed conditions  A review of such processes may be found in Nielsen, A T , Houlihahn,
W J , *Org  React* **16**, 1968, p 1-444  In particular the method described by Wattanasin, S
10  and Murphy, S , *Synthesis* (1980) 647 has been found quite successful  The reaction may
suitably be carried out in protic organic solvents, such as lower alcohols (e g  methanol,
ethanol, or tert-butanol), or lower carboxylic acids (formic, glacial acetic, or propionic
acid), or in aprotic organic solvents such as ethers (e g  tetrahydrofuran, dioxane, or
diethyl ether), liquid amides (e g  dimethylformamide or hexamethylphosphordiamide),
15  dimethylsulfoxide, or hydrocarbons (e g  toluene or benzene), or mixtures of such
solvents  When carrying out the reaction under base catalysed conditions, the catalyst may
be selected from sodium, lithium, potassium, barium, calcium, magnesium, aluminum,
ammonium, or quaternary ammonium hydroxides, lower alkoxides (e g  methoxides,
ethoxides, tert-butoxides), carbonates, borates, oxides, hydrides, or amides of lower
20  secondary amines (e g  diisopropyl amides or methylphenyl amides)  Primary aromatic
amines such as aniline, free secondary amines such as dimethyl amine, diethyl amine,
piperidine, or pyrrolidine as well as basic ion exchange resins may also be used

Acid catalysts may be selected from hydrogen chloride, hydrogen bromide, hydrogen
25  iodide, sulfuric acid, sulfonic acids (such as paratoluenesulfonic or methanesulfonic acid),
lower carboxylic acids (such as formic, acetic or propionic acid), lower halogenated
carboxylic acids (such as trifluoroacetic acid), Lewis acids (such as $BF_3$, $POCl_3$, $PCl_5$, or
$FeCl_3$), or acid ion exchange resins

30  A drawback of the base catalysed condensation is the poor yield obtained if the aromatic
ring in which the ketone or the aldehyde or both is substituted with one or more hydroxy
groups  This drawback can be overcome by masking the phenolic group as described by T
Hidetsugu et al  in EP 0 370 461  Deprotection is easily performed by mineral acids such as
hydrochloric acid
35
The reaction is typically carried out at temperatures in the range of 0-100°C, e g  at room
temperature  Reaction times are typically from 30 min to 24 hours

The starting materials for the synthesis (acetophenone and aldehyde), may be obtained
40  from commercial sources or may be synthesised according to well-known methods  The
diamino-benzaldehydes can be synthesized by Palladium catalysed reaction of bromo-
benzaldehyde diethyl acetal and diamine followed by acidic work up  Alternatively, the 2-
diamino-benzaldehydes can be prepared by nucleophilic aromatic substitution using 2-
fluorobenzaldehyde and diamine  The diamino-acetophenones can be synthesized by

Palladium catalysed reaction of bromoacetophenone ketal and diamine followed by acidic work up Alternatively the 2'-diamino-acetophenones can be synthesized by nucleophilic aromatic substitution using 2'-flouroacetophenone and diamine

5  Compounds of the general formula I in which V is -C≡C- may be prepared by reacting an activated derivative of a carboxylic acid of the general formula

$$Y^1(X^1)-Ar^1-COOH$$

10  with an ethyne derivative

$$H-C≡C-Ar^2-(X^2)Y^2$$

wherein $Ar^1$, $Ar^2$, $X^1$, $X^2$, $Y^1$, and $Y^2$ refers to the definitions given elsewhere herein

15  Reactions of this type are described by Tohda, Y , Sonogashihara, K , Haghara, N , *Synthesis* **1977**, p 777-778 It is contemplated that the activated derivative of the carboxylic acid may be an activated ester, an anhydride or, preferably, an acid halogenide, in particular the acid chloride The reaction is normally carried out using the catalysts

20  described by Tohda, Y *et al* cited above, namely copper(I)iodide/triphenylphosphine-palladium dichloride The reaction is suitably carried out in triethylamine, a mixture of triethylamine and pyridine or triethylamine and toluene under a dry inert atmosphere such as nitrogen or argon The reaction is generally carried out at reduced temperature such as in the range from -80°C to room temperature, the reaction time typically being from 30

25  minutes to 6 hours

In the above reactions, it may be preferred or necessary to protect various sensitive or reactive groups present in the starting materials to prevent said groups from interfering with the reactions Such protection may be carried out in a well-known manner, e g as

30  described in "Protective Groups in Organic Chemistry" by Wuts and Greene, Wiley-Interscience, ISBN 0471160199, 3nd edition (May 15, 1999) For example, in the reaction between the activated acid derivative and the acetylene derivative, a hydroxy group on $Ar^1$ and/or $Ar^2$ may be protected in the form of the methoxymethyl ether, N,N-dimethylcarbamoyl ester, or allyl ether The protecting group may be removed after the

35  reaction in a manner known *per se*

The ethyne derivative may be prepared by standard methods, e g as described by Nielsen, S F Et al , Bioorg Med Chem 6, pp 937-945 (1998) The carboxylic acids may likewise be prepared by standard procedures, e g as described by Nakayama, T Chem Pharm

40  Bull 41, pp 117-125 (1993)

Compounds of the general formula I in which V is $-CH_2-CH_2-$ can be prepared by ionic hydrogenation of the corresponding $\alpha,\beta$-unsaturated compound where V is -CH=CH- as it has been described by the inventors in Nielsen, S F et al Tetrahedron, 53, pp 5573-5580

(1997) Alternatively, it is possible to prepare such compounds from the corresponding flouro (or bromo) chalcones using $H_2/Pt$ followed by nucleophilic aromatic amination (see Figure 3)

5  Further possible synthetic routes for the preparation of the saturated variants are described in "Advanced Organic Chemistry" by Jerry March, 3rd ed (especially chapter 15, pages 691-700) and references cited therein Thus, it is possible to obtain a large variety of compounds of the 1,3-bis-aromatic-propan-1-one type from the corresponding prop-2-en-1-ones

10

Medical uses

It has been demonstrated herein (see the Examples section) that the novel compound have interesting properties as bacteriostatic, bacteriocidal and antiparasitic agents It is of course possible that the compounds also have other interesting properties to be utilised in

15  the medical field

Thus, the present invention provides a compound (chalcone derivative) as defined herein for use as a drug substance

20  In particular, the chalcone derivative may be used for the treatment of bacterial infections in a mammal in need thereof Such bacterial infection may be caused by common Gram-positive and Gram-negative pathogens as well as microaerophilic and anaerobic bacteria As a particularly relevant example of a bacteria against which chalcone derivatives have effect can be mentioned antibiotic-sensitive and -resistant strains of *S aureus* and

25  *E faecium* Other examples common causes of community acquired and nosocomial respiratory infections including *S pneumoniae, S pyogenes* and members of *Enterobacteriaceae* (e g *E coli*), microaerophilic bacteria associated with gastric disease (e g *Helicobacter pylori*) and pathogenic anaerobic bacteria (e g *Bacteroides fragilis* and *Clostridium species*)

30

Also, the chalcone derivatives can be used for the treatment of infections caused by protozoa in a mammal Examples of infections are those caused by a protozoa selected from *Plasmodium falciparum, Plasmodium vivax, Plasmodium ovale* and *Plasmodium malariae*

35

Furthermore, the chalcone derivatives can be used for the preparation of a pharmaceutical composition for the treatment of infections in a mammal caused by *Leishmania spp* Such infections may be cutaneous and/or visceral

40  The chalcone derivatives are typically formulated in a pharmaceutical composition prior to use as a drug substance

Formulation of pharmaceutical compositions

The administration route of the compounds (diamino-functional chalcones) as defined herein may be any suitable route which leads to a concentration in the blood or tissue corresponding to a therapeutic concentration Thus, e g , the following administration
5 routes may be applicable although the invention is not limited thereto the oral route, the parenteral route, the cutaneous route, the nasal route, the rectal route, the vaginal route and the ocular route It should be clear to a person skilled in the art that the administration route is dependant on the particular compound in question, particularly, the choice of administration route depends on the physico-chemical properties of the
10 compound together with the age and weight of the patient and on the particular disease or condition and the severity of the same

The compounds as defined herein may be contained in any appropriate amount in a pharmaceutical composition, and are generally contained in an amount of about 1-95% by
15 weight of the total weight of the composition The composition may be presented in a dosage form which is suitable for the oral, parenteral, rectal, cutaneous, nasal, vaginal and/or ocular administration route Thus, the composition may be in form of, e g , tablets, capsules, pills, powders, granulates, suspensions, emulsions, solutions, gels including hydrogels, pastes, ointments, creams, plasters, drenches, delivery devices, suppositories,
20 enemas, injectables, implants, sprays, aerosols and in other suitable form

The pharmaceutical compositions may be formulated according to conventional pharmaceutical practice, see, e g , "Remington's Pharmaceutical Sciences" and "Encyclopedia of Pharmaceutical Technology", edited by Swarbrick, J & J C Boylan,
25 Marcel Dekker, Inc , New York, 1988 Typically, the compounds defined herein are formulated with (at least) a pharmaceutically acceptable carrier or exipient Pharmaceutically acceptable carriers or exipients are those known by the person skilled in the art

30 Thus, the present invention provides a pharmaceutical composition comprising a compound as defined herein in combination with a pharmaceutically acceptable carrier

Pharmaceutical compositions according to the present invention may be formulated to release the active compound substantially immediately upon administration or at any
35 substantially predetermined time or time period after administration The latter type of compositions are generally known as controlled release formulations

In the present context, the term "controlled release formulation" embraces i) formulations which create a substantially constant concentration of the drug within the body over an
40 extended period of time, ii) formulations which after a predetermined lag time create a substantially constant concentration of the drug within the body over an extended period of time, iii) formulations which sustain drug action during a predetermined time period by maintaining a relatively, constant, effective drug level in the body with concomitant minimization of undesirable side effects associated with fluctuations in the plasma level of

the active drug substance (sawtooth kinetic pattern), iv) formulations which attempt to localize drug action by, e g , spatial placement of a controlled release composition adjacent to or in the diseased tissue or organ, v) formulations which attempt to target drug action by using carriers or chemical derivatives to deliver the drug to a particular target cell type

5

Controlled release formulations may also be denoted "sustained release", "prolonged release", "programmed release", "time release", "rate-controlled" and/or "targeted release" formulations

10 Controlled release pharmaceutical compositions may be presented in any suitable dosage forms, especially in dosage forms intended for oral, parenteral, cutaneous nasal, rectal, vaginal and/or ocular administration  Examples include single or multiple unit tablet or capsule compositions, oil solutions, suspensions, emulsions, microcapsules, microspheres, nanoparticles, liposomes, delivery devices such as those intended for oral, parenteral,

15 cutaneous, nasal, vaginal or ocular use

Preparation of solid dosage forms for oral use, controlled release oral dosage forms, fluid liquid compositions, parenteral compositions, controlled release parenteral compositions, rectal compositions, nasal compositions, percutaneous and topical

20 compositions, controlled release percutaneous and topical compositions, and compositions for administration to the eye can be performed essentially as described in the applicant's earlier International application No  WO 99/00114, page 29, line 9, to page 40, line 3  Also, and more generally, the formulation and preparation of the above-mentioned compositions are well-known to those skilled in the art of pharmaceutical formulation

25 Specific formulations can be found in "Remington's Pharmaceutical Sciences"

Dosages

The compound are preferably administered in an amount of about 0 1-50 mg per kg body weight per day, such as about 0 5-25 mg per kg body weight per day

30

For compositions adapted for oral administration for systemic use, the dosage is normally 2 mg to 1 g per dose administered 1-4 times daily for 1 week to 12 months depending on the disease to be treated

35 The dosage for oral administration for the treatment of parasitic diseases is normally 1 mg to 1 g per dose administered 1-2 times daily for 1-4 weeks, in particular the treatment of malaria is to be continued for 1-2 weeks whereas the treatment of leishmaniasis will normally be carried out for 3-4 weeks

40 The dosage for oral administration for the treatment of bacterial diseases is normally 1 mg to 1 g per dose administered 1-4 times daily for 1 week to 12 months, in particular, the treatment of tuberculosis will normally be carried out for 6-12 months

The dosage for oral administration of the composition in order to prevent diseases is normally 1 mg to 75 mg per kg body weight per day  The dosage may be administered once or twice daily for a period starting 1 week before the exposure to the disease until 4 weeks after the exposure

5

For compositions adapted for rectal use for preventing diseases, a somewhat higher amount of the compound is usually preferred, i e  from approximately 1 mg to 100 mg per kg body weight per day

10  For parenteral administration, a dose of about 0 1 mg to about 50 mg per kg body weight per day is convenient  For intravenous administration a dose of about 0 1 mg to about 20 mg per kg body weight per day administered for 1 day to 3 months is convenient  For intraarticular administration a dose of about 0 1 mg to about 20 mg per kg body weight per day is usually preferable  For parenteral administration in general, a solution in an

15  aqueous medium of 0 5-2% or more of the active ingredients may be employed

For topical administration on the skin, a dose of about 1 mg to about 5 g administered 1-10 times daily for 1 week to 12 months is usually preferable

20  In many cases, it will be preferred to administer the compound defined herein together with another antiparasitic, antimycotic or antibiotic drug, thereby reducing the risk of development of resistance against the conventional drugs, and reducing the amount of each of the drugs to be administered, thus reducing the risk of side effects caused by the conventional drugs  Important aspects of this is the use of the compound against

25  Leishmania, where the compound I is combined with another antileishmanial drug, or the antimalarial use of the compound I where the compound I is used together with another antimalarial drug

Method of prediction

30

In a separate aspect, the present invention also provides a method of predicting whether a chemical compound has a potential inhibitory effect against a microorganism selected from Helicobacter pylori and Plasmodium falciparum, said method comprising preparing a mixture of a dihydroorotate dehydrogenase, a substrate for dihydroorotate dehydrogenase

35  and the chemical compound, measuring the enzymatic activity of dihydroorotate dehydrogenase (A), comparing the enzymatic activity of dihydroorotate dehydrogenase (A) with the standard activity of dihydroorotate dehydrogenase (B) corresponding to the activity of a dihydroorotate dehydrogenase in a similar sample, but without the chemical compound, predicting that the chemical compound has a potential inhibitory effect against

40  Helicobacter pylori and Plasmodium falciparum if A is significantly lower than B

The method can be performed as described under DHODH Assay in the Examples section  It should be noted that the method is not only applicable for the chalcone derivatives defined herein, but can be generally applied to predict the potential inhibitory effect of any

compound Preferably, however, the chemical compound is a chalcone derivative, e g a chalcone derivative as defined herein

## EXAMPLES

Preparation of compounds

5 The general method for the preparation of the A ring or B ring having the diamino-functional group is illustrated in Figure 1

### General procedure A

10 Amination of bromobenzaldehydes

Bromobenzaldehyde diethyl acetal (40 mmol), amine (48 mmol), $Pd_2(dba)_3$ (0 2 mmol, 1 mol% Pd), rac-BINAP (0 6 mmol) and Na-t-OBu (68 mmol) was stirred in degassed toluene (60 mL) at 80°C for 18 h The darkbrown mixture was poured into icecold
15 hydrochloric acid (1 M, 200 mL) and stirred vigorously for 2 hours at 25°C The solution was cooled to 0°C and pH was adjusted to 13 using 6M NaOH(aq) and extracted with $Et_2O$ (4 x 100 mL) The organic phase was dried ($K_2CO_3$) and the solvent was removed under reduced pressure The resulting crude oil purified by flash chromatography using 5% $Et_3N$ in EtOAc

20

### General procedure B

Nucleophilic aromatic substitution on Fluorobenzaldehyde

A stirred solution of fluoro-benzaldehyde (49 3 mmol) in dry DMF (50 mL) was added
25 $K_2CO_3$ (10 2 g, 74 0 mmol) and amine (74 mmol) and left overnight at 100°C The reaction mixture was cooled to room temperature, added water (100 mL) and extracted with ether (3 x 50 mL) The combined organic phases was washed with water and dried ($Na_2SO_4$) Evaporation in vacuo and recrystallization (heptane) gave the product

30

### General Procedure C

Amination of bromoacetophenones

3'- or 4'-bromoacetophenone was converted into the corresponding cyclic ketal A solution
35 of 3- or 4-bromoacetophenone (0 10 mol), 1,3-propandiol (0 12 mol) and p-TsOH (0 1 g) in toluene (200 mL) was heated and water was azeotropically removed using a Dean-Stark water-separator After 18 hours, the solution was washed with 5% $Na_2CO_3$ (100 ml), dried ($K_2CO_3$) and the solvent was removed under reduced pressure According to ^{1}HNMR the ketals was pure enough for further reaction

40

3'- or 4'-bromoacetophenone ketal (40 mmol), amine (48 mmol), Pd₂(dba)₃ (0 2 mmol, 1 mol% Pd), rac-BINAP (0 6 mmol) and Na-t-OBu (68 mmol) was stirred in degassed toluene (60 mL) at 80°C for 18 h The darkbrown mixture was poured into icecold hydrochloric acid (1 M, 200 mL) and stirred vigorously for 2 hours at 25°C The solution
5 was cooled to 0°C and pH was adjusted to 13 using 6M NaOH(aq) and extracted with Et₂O (4 x 100 mL) The organic phase was dried (K₂CO₃) and the solvent was removed under reduced pressure The resulting crude oil purified by flash chromatography using 5% Et₃N in EtOAc

10 **General procedure D**

Nucleophilic aromatic substitution on Fluoroacetophenone

A mixture of Fluoroacetophenone (40 mmol), amine (50 mmol), K₂CO₃ (50 mmol) was
15 refluxed in dry DMF (20 mL) under an argon atmosphere for 18 h The DMF was removed using an oilpump and water (50 mL) was added to the residue The water phase was extracted with Et₂O (2 x 100 mL) and the organic phase was dried (K₂CO₃) and evaporated to yellow oil, which was pure enough for further reaction

20 **General procedure E**

Preparation of alkyl aminomethyl acetophenones

To a solution of (2-methyl-[1,3]dioxan-2-yl) benzaldehyde (165 mmol) and amine (247 mmol) in dry THF (1 5 L) was added sodium triacetoxyborohydride (257mmol) under
25 argon The resulting suspension was stirred at room temperature for 18 hr A solution of sodium hydroxide (2M) was added and stirring was continued for approximately 30 min, before the mixture was acidified using HCl (6M) The mixture was stirred for 1 hr and extracted with diethyl ether, which was discarded The pH of the aqueous phase was adjusted to 11 - 14 using sodium hydroxide and extracted again with diethyl ether The
30 latter organic phase, was dried over sodium sulphate, filtered and evaporated to give the title products, which were used without further purification

**General procedure F**

Preparation of alkyl aminomethyl benzaldehydes

35
To a solution of diethoxymethyl benzaldehyde (16 5 mmol) and amine (24 7 mmol) in dry THF (150 mL) was added sodium triacetoxyborohydride (25 7mmol) under argon The resulting suspension was stirred at room temperature for 6-18 hr A solution of sodium hydroxide (2M) was added and stirring was continued for approximately 30 min, before the
40 mixture was acidified using HCl (6M) The mixture was stirred for 1 hr and extracted with diethyl ether, which was discarded The pH of the aqueous phase was adjusted to 11 - 14

using sodium hydroxide and extracted again with diethyl ether The latter organic phase, was dried over sodium sulphate, filtered and evaporated to give the title products, which were used without further purification

## 5 General procedure G

Preparation of (2-dimethylaminoethoxy)-benzaldehydes

A stirred solution of hydroxybenzaldehyde (59 7 mmol) in dry toluene (200 mL) and DMSO
10 (1 mL) was added 60% NaH (60 mmol) under ice cooling The reaction was slowly heated to room temperature 2-Dimethylaminoethylchloride, HCl (15 9 g, 110 mmol) dissolved in water (50 mL) was added NaOH (4 4 g, 110 mmol) and the aqueous phase was extracted with toluene (3 x 30 mL) The combined organic phases were dried (Na$_2$SO$_4$) and slowly added to the reaction The solution was heated to 90°C for 16 h The reaction mixture was
15 cooled to room temperature and washed with water (3 x 100 mL), 2N NaOH (100 mL) and dried (Na$_2$SO$_4$) Evaporation in vacuo gave the title products

## General procedure H

Preparation of biaryl carbaldehydes

20 A solution of Na$_2$CO$_3$ (44 mmol) in water (20 mL) was added to a solution of bromobenzaldehyde (14 7 mmol) and (hetero)arylboronic acid (17 6 mmol) in DME (40 mL) The mixture was flushed with argon for 2 minutes followed by addition of Pd(PPh$_3$)$_2$Cl$_2$ (310 mg, 3 mol %) The reaction was heated at reflux and left overnight under an atmosphere of argon The reaction was cooled, 2M Na$_2$CO$_3$ was added, and the mixture
25 was extracted with EtOAc (3 x 20 mL) The title products were purified by flash chromatography

## General procedure I

30 Amino-acylation of amino-acetophenones and amino-benzaldehydes

A solution of amino-acetophenone/benzaldehyde (25 mmol) in THF (100 mL) was added chloroacyl chloride (30 mmol) The mixture was stirred for 30 min, poured into icecold 2M NaOH (aq) and extracted with Et$_2$O The organic phase was dried and the solvent was
35 removed under reduced pressure giving the pure product A solution of the product (10 mmol) and triethyl amine (30 mmol) in ethanol was added amine (20 mmol) and the mixture was refluxed for 4 hours Ethanol was removed under reduced pressure and the product was dissolved in EtOAc and washed with 2M NaOH (aq) EtOAc was removed under reduced pressure giving the product as a pure oil .

40

## General procedure J

Synthesis of (amino-)chalcones

To a solution of an acetophenone (2 mmol) and a benzaldehyde (2 mmol) in 96% EtOH
5 (10 mL) was added 8M NaOH (0 3 mL), and the mixture was stirred for 3-18 hours at
25°C The mixture was evaporated on Celite® and the product was isolated by flash
chromatography The aminochalcone was dissolved in MeOH Et₂O (1 9 v/v, 10 mL) and a
solution of fumaric acid or oxalic acid in MeOH Et₂O (1 9 v/v) was added The salt was
filtered off and recrystallised from MeOH or MeCN Some aminochalcones did not undergo
10 saltformation, and was isolated as the free base The purity was >95% determined by
HPLC and the molecular weight was determined by LC-MS

## General procedure K
15

Synthesis of (hetero)aryl chalcones from bromo-chalcones

A solution of bromo-chalcone (0 92 mmol) and (hetero)aryl boronic acid (1 11 mmol) in
DME (10 mL) was added a solution of Na₂CO₃ (290 mg, 2 8 mmol) in water (5 mL) The
20 mixture was bubbled through with argon for 2 minutes followed by addition of Pd(PPh₃)₂Cl₂
(19 mg, 3 mol %) The reaction was heated to reflux and left overnight under an
atmosphere of argon The solution was cooled, added 2M Na₂CO₃, extracted with ether (3 x
20 mL) and purified by column chromatography

25

## General procedure L

Synthesis of fluoro-(or bromo-)dihydrochalcones

30 Fluoro- (or bromo-)chalcone was dissolved in EtOAc (100 mL), and 5% Pt/C (100 mg) was
added and the mixture was hydrogenated at 1 bar H₂ The addition of hydrogen was
stopped when the theoretical amount was absorbed (1 eqv H₂) The mixture was filtered
and evaporated leaving the product as an oil The product was purified by column
chromatography or crystallisation
35

## General procedure M

Synthesis of fluoro- (or bromo)-diamino-dihydrochalcones
40
A mixture of fluoro-dihydrochalcone (4 5 mmol), amine (6 0 mmol), K₂CO₃ (0 83 g, 6 0
mmol) was refluxed in dry degassed DMF (6 mL) for 24 h The red mixture was poured
into water (100 mL) and extracted with EtOAc (3 x 30 mL), dried (K₂CO₃) and the solvent
was removed under reduced pressure The resulting dark oil was purified by column
45 chromatography (SiO₂) using EtOAc as eluent

### 5-Dibutylamino-2-methoxy-benzaldehyde

5  **I-001** 2-(5-Bromo-2-methoxy-phenyl)-[1,3]dioxane

A solution of 5-bromo-*o*-anisaldehyde (25 g, 116 mmol), 1,3-propandiol (9 mL, 125 mmol), *p*-toluenesulphonic acid (0 1 g) in toluene (150 mL) was heated and water was azeotropically removed using a Dean-Stark water-separator After 18 hours, the solution was washed with 5% $Na_2CO_3$ (100 ml), dried ($K_2CO_3$) and the solvent was removed under

10  reduced pressure The acetal was purified by vacuumdistillation and isolated as an clear oil bp 126-130°C/0 05 mbar

$^1$H-NMR(300 MHz, CDCl$_3$) δ 7 74 (d, 1H), 7 38 (dd, 1H), 6 75 (d, 1H), 5 82 (s, 1H), 4 28-4 20 (m, 2H), 4 04-3 92 (m, 2H), 3 80 (s, 3H), 2 33-2 13 (m, 1H), 1 48-1 38 (m, 1H)

15  **I-002** 5-Dibutylamino-2-methoxy-benzaldehyde

2-(5-Bromo-2-methoxy-phenyl)-[1,3]dioxane (40 mmol), di-*n*-butylamine (48 mmol), Pd$_2$(dba)$_3$ (0 2 mmol, 1 mol% Pd), P(*o*-tol)$_3$ (0 6 mmol) and Na-*t*-OBu (68 mmol) was stirred in degassed toluene (60 mL) at 80°C for 18 h The darkbrown mixture was poured into icecold hydrochloric acid (1 M, 200 mL) and stirred vigorously for 2 hours at 25°C The

20  solution was cooled to 0°C and pH was adjusted to 9 using 6M NaOH(aq) and extracted with Et$_2$O (4 x 100 mL) The organic phase was dried (Na$_2$SO$_4$) and the solvent was removed under reduced pressure The resulting crude oil purified by flash chromatography using EtOAc/*n*-heptane (1 4, v/v) as eluent The product was isolated as a yellow oil in 46% yield

25
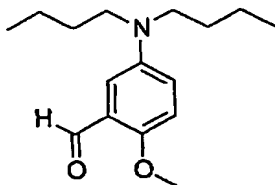


$^1$H-NMR(300 MHz, CDCl$_3$) δ 9 98 (s, 1H), 7 15 (d, 1H), 6 92 (d, 1H), 6 79 (dd, 1H), 3 80 (s, 3H), 3 25 (t, 4H), 1 55-1 40 (m, 4H), 1 40-1 25 (m, 4H), 0 91 (t, 6H)

30

**I-003** 2-[(2-Dimethylamino-ethyl)-methyl-amino]benzaldehyde



35
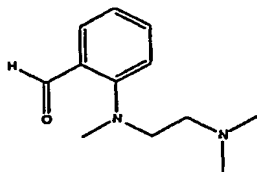
General procedure B gave the title compound as a yellow oil in 56% yield  ref 1
^{1}H-NMR(300 MHz, CDCl$_3$)  δ 10 29 (s, 1H), 7 82-7 75 (dd, 1H), 7 53-7 43 (td, 1H), 7 13 (d, 1H), 7 05 (t, 1H), 3 25 (t, 2H), 2 92 (s, 3H), 2 52 (t, 2H), 2 22 (s, 6H)

5

**I-004**  3-(2-Dimethylamino-ethylamino)benzaldehyde
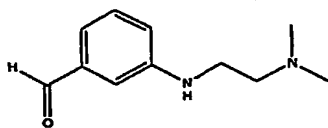


General procedure A gave the title compound as a yellow oil in 52% yield
10  ^{1}H-NMR(300 MHz, CDCl$_3$)  δ 9 81 (s, 1H), 7 65 (d, 2H), 6 60 (d, 2H), 5 11 (s, br, 1H), 3 20-3 14 (m, 2H), 2 56 (t, 2H), 2 26 (s, 6H)

**I-005**  3-[(2-Dimethylamino-ethyl)-methyl-amino]benzaldehyde
15
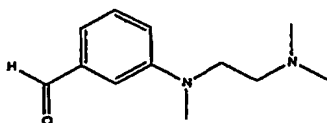


General procedure A gave the title compound as a yellow oil in 90% yield

^{1}H-NMR(300 MHz, CDCl$_3$)  δ 9 91 (s, 1H), 7 35 (t, 1H), 7 12-7 05 (m, 2H), 7 00-6 93 (dd,
20  1H), 3 56 (t, 2H), 3 05 (s, 3H), 2 55 (t, 2H), 2 38 (s, 6H)

**I-006**  4-[(2-Dimethylamino-ethyl)-methyl-amino]benzaldehyde
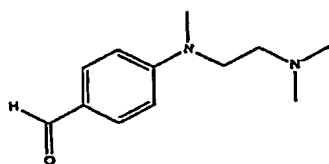


25
General procedure A gave the title compound as a yellow oil in 66% yield ref  2

^{1}H-NMR(300 MHz, CDCl$_3$)  δ 9 73 (s, 1H), 7 73 (d, 2H), 6 71 (d, 2H), 3 54 (t, 2H), 3 08 (s, 3H), 2 50 (t, 2H), 2 30 (s, 6H)
30

**I-007**  3-(Pyridin-3-ylamino)-benzaldehyde

24
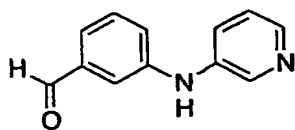


General procedure A gave the title compound as white crystal in 69& yield
$^1$H-NMR(300 MHz, DMSO-d$_6$)  δ 9 94 (s, 1H), 8 67 (s, 1H), 8 40 (d, 1H), 8 11 (dd, 1H),
7 58-7 50 (m, 2H), 7 47 (d, 1H), 7 43-7 35 (m, 2H), 7 29 (dd, 1H)

5

**I-008**  4-(2-Dimethylamino-ethylamino) benzaldehyde
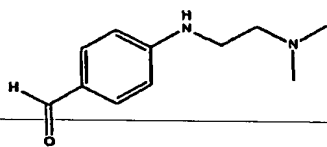


10  General procedure A gave the title compound as a yellow oil in 74% yield ref  2

$^1$H-NMR(300 MHz, CDCl$_3$)  δ 9 71 (s, 1H), 7 68 (d, 2H), 6 61 (d, 2H), 5 08 (s, br, 1H),
3 24-3 18 (m, 2H), 2 57 (t, 2H), 2 26 (s, 6H)

15

**I-009**  5-Bromo-2-(4-methyl-piperazin-1-yl)-benzaldehyde
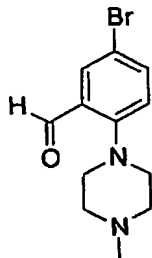


20  General procedure B gave the title compound as yellow crystals in 62% yield
$^1$H NMR (CDCl$_3$) δ 10 24 (s, 1H), 7 91 (d, 1H), 7 61 (dd, 1H), 7 02 (d, 1H), 3 11 (t, 4H),
2 63 (t, 4H), 2 39 (s, 3H)

25

**I-010**  1-{4-[(2-Dimethylamino-ethyl)-methyl-amino]-phenyl}ethanone
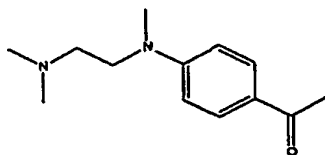


General procedure C gave the title compound as an yellow oil in 62% yield ref  3

$^1$H-NMR(300 MHz, CDCl$_3$) δ 7 72 (d, 2H), 6 73 (d, 2H), 3 53 (t, 2H), 3 08 (s, 3H), 2 50 (t, 2H), 2 48 (s, 3H), 2 30 (s, 6H)

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5  **I-011**  1-[4-(2-Dimethylamino-ethylamino)-phenyl]ethanone
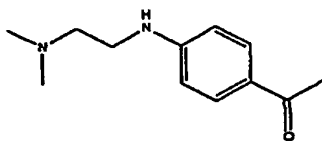


General procedure C gave the title compound as a yellow oil in 92% yield ref 3
$^1$H-NMR(300 MHz, CDCl$_3$) δ 7 80 (d, 2H), 6 54 (d, 2H), 5 29 (s, br, 1H), 3 33-3 24 (m,
10  2H), 2 57 (t, 2H), 2 56 (s, 3H), 2 31 (s, 6H)

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**I-012**  1-[4-(3-Dimethylamino-propylamino)-phenyl]ethanone



15
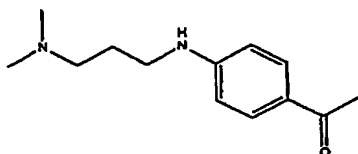
General procedure C gave the title compound as a yellow oil in 56% yield
$^1$H-NMR(300 MHz, CDCl$_3$) δ 7 81 (d, 2H), 6 54 (d, 2H), 5 31 (s, br, 1H), 3 25 (t, 2H), 2 48
(s, 3H), 2 41 (t, 2H), 2 25 (s, 6H), 1 79 (m, 2H)

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20

**I-013**  1-[3-(2-Dimethylamino-ethylamino)-phenyl]ethanone
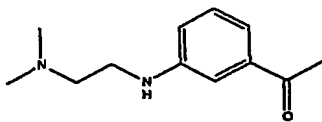


General procedure C gave the title compound as a yellow oil in 73% yield

25

$^1$H-NMR(300 MHz, CDCl$_3$) δ 7 28-7 18 (m, 3H), 6 85-6 78 (m, 1H), 4 45 (s, br, 1H), 4 10-
3 23 (m, 2H), 2 59-2 52 (m, 5H), 2 25 (s, 6H)

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30  **I-014**  1-{3-[(2-Dimethylamino-ethyl)-methyl-amino]-phenyl}ethanone
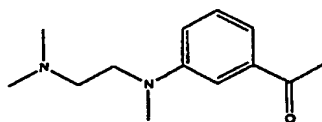
General procedure C gave the title compound as a yellow oil in 62% yield
$^1$H-NMR(300 MHz, CDCl$_3$)  δ 7 30-7 18 (m, 3H), 6 82-6 78 (m, 1H), 3 56 (t, 2H), 3 05 (s, 3H), 2 55 (t, 2H), 2 48 (s, 3H), 2 38 (s, 6H)

5

**I-015**  1-[2-(2-Dimethylamino-ethylamino)-phenyl]ethanone
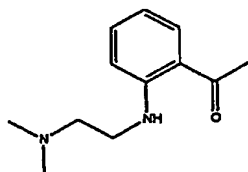


General procedure D gave the title compound as a yellow oil in 58% yield
10   $^1$H-NMR(300 MHz, CDCl$_3$)  δ 8 95 (s, br, 1H), 7 76-7 71 (dd, 1H), 7 38-7 31 (d, 1H), 6 73-6 66 (d, 1H), 6 61-6 55 (td, 1H), 3 33-3 24 (m, 2H), 2 58 (t, 2H), 2 56 (s, 3H), 2 30 (s, 6H)

15  **I-016**  1-{2-[(2-Dimethylamino-ethyl)-methyl-amino]-phenyl}ethanone
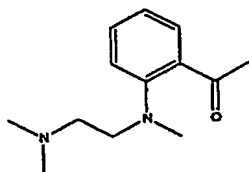


General procedure D gave the title compound as a yellow oil in 93 % yield
$^1$H-NMR(300 MHz, CDCl$_3$)  δ 7 42-7 32 (m, 2H), 7 07 (d, 1H), 7 70-6 93 (td, 1H), 3 17 (t,
20  2H), 2 80 (s, 3H), 2 61 (s, 3H), 2 49-2 42 (m, 2H), 2 20 (s, 6H)

**I-017**  1-[2-(3-Dimethylamino-propylamino)-phenyl]ethanone



25
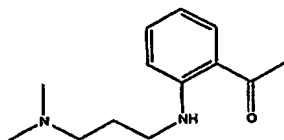
General procedure D gave the title compound as a yellow oil in 45% yield
$^1$H-NMR(300 MHz, CDCl$_3$)  δ 8 91 (s, br, 1H), 7 74-7 70 (dd, 1H), 7 38-7 31 (d, 1H), 6 73-6 65 (d, 1H), 6 61-6 55 (td, 1H), 3 25 (t, 2H), 2 48 (s, 3H), 2 41 (t, 2H), 2 25 (s, 6H), 1 79 (m, 2H)

30

**I-018**  5-Bromo-2-(2-dimethylamino-ethoxy)-benzaldehyde
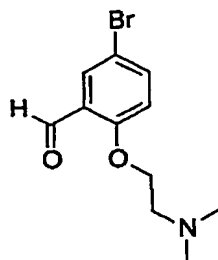
General procedure G gave the title compound as a yellow oil in 65 % yield

¹H NMR (CDCl₃)  δ 10 43 (s, 1H), 7 94 (d, 1H), 7 63 (dd, 1H), 6 92 (d, 1H), 4 19 (t, 2H),

5   2 81 (t, 2H), 2 37 (s, 6H)

10  **I-019**  4-(2-Dimethylamino-ethoxy)-biphenyl-3-carbaldehyde
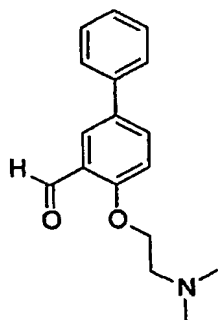


General procedure H gave the title compound as yellow crystals in 57% yield

15  ¹H NMR (CDCl₃)  δ 10 48 (s, 1H), 8 01 (d, 1H), 7 71 (dd, 1H), 7 49 (d, 1H), 7 36 (t, 2H),
    7 26 (t, 1H), 7 00 (d, 1H), 4 18 (t, 2H), 2 77 (t, 2H), 2 31 (s, 6H)

20  **I-020**  1-[2-(4-Methyl-piperazin-1-ylmethyl)-phenyl]-ethanone
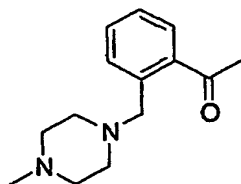


General procedure E gave the title compound as a brown oil in 78% yield

    ¹H-NMR (CDCl₃)  δ 7 42-7 29 (m, 4H), 3 65 (s, 2H), 2 54 (s, 3H), 2 43 (b, 8H), 2 27 (s,

25  3H)

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**I-021** 2-(4-Methyl-piperazin-1-ylmethyl)-benzaldehyde



5
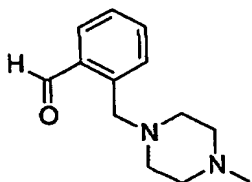
General procedure F gave the title compound as a brown oil in 80 % yield
¹H-NMR(300 MHz, CDCl3)  δ 10 41 (s, 1H), 7 87 (d, 1H), 7 51 (dt, 1H)7 41 (t, 1H), 7 38
(d, 1H), 3 81 (s, 2H), 2 6-2 3 (m, 8H), 2 27 (s, 3H)

10

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**I-022** 4-Diethylaminomethyl-benzaldehyde
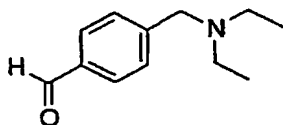


15  General procedure F gave the title compound as a brown oil in 74% yield

¹H-NMR (CDCl₃)  δ 10 02 (s, 1H), 7 85 (d, 2H), 7 55 (d, 2H), 3 66 (s, 2H), 2 56 (k, 4H),
1 07 (t, 6H)

20

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**I-023**  N-(3-Acetyl-phenyl)-2-dimethylamino-acetamide
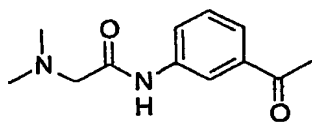


25
General procedure I gave the title compound as a brown oil in 85% yield
¹H-NMR(300 MHz, CDCl3)  δ 9 31 (s, 1H), 8 05 (m, 2H), 7 72 (dt, 1H), 7 46 (t, 1H), 3 11
(s, 2H), 2 62 (s, 3H), 2 41 (s, 6H)

30

5-(1,1-Dimethyl-allyl)-2-methoxy-benzaldehyde

●                    ●
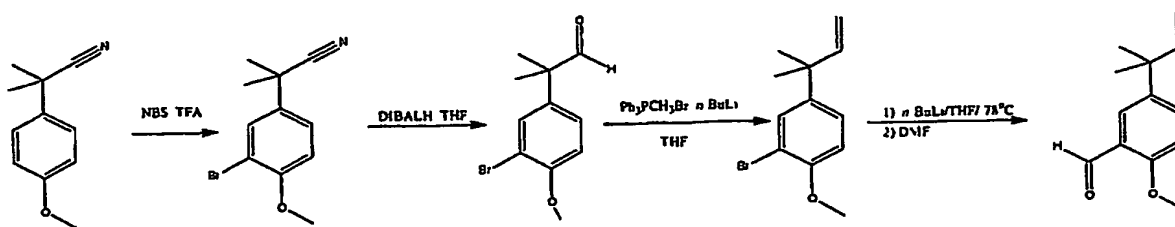
5  **I-024** 2-(3-Bromo-4-methoxy-phenyl)-2-methyl-propionitrile
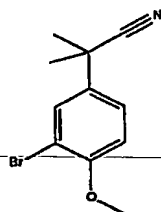


A solution of 2-(4-methoxy-phenyl)-2-methyl-propionitrile (17 5 g, 0 10 mol) in TFA (80
10  mL) was cooled to 0°C  N-bromosuccinimide (17 8 g, 0 10 mol) was added in small
portions keeping the temperature below 5°C  The orange solution was stirred for 2h/25°C
and evaporated to dryness  Water (200 mL) was added and the mixture was stirred
vigorously for 1 h  The crude product was filtered off and recrystallized from boiling MeOH
The pure product was isolated as white needles  Yield  19 3 g (76%)  GCMS  > 99%
15  $^1$H-NMR(300 MHz, DMSO-$d_6$)  δ 7 68 (d, 1H), 7 50 (dd, 1H), 7 16 (d, 1H), 3 86 (s, 3H),
1 70 (s, 6H)

**I-025**  2-(3-Bromo-4-methoxy-phenyl)-2-methyl-propionaldehyde
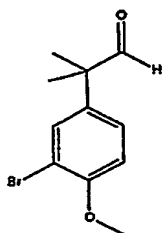


20

A solution of 2-(3-bromo-4-methoxy-phenyl)-2-methyl-propionitrile (12 71 g, 0 050 mol)
in dry THF (100 mL) was cooled to −10°C under argon  DIBALH (1M in THF, 100 mL, 0 10
mol) was added keeping the temperature below 0°C  The mixture was stirred for 30
25  min/0°C  and then  2  h/25°C  The clear solution was carefully poured into icecold
hydrochloric acid (2M, 100 mL)  The THF was removed under reduced pressure to give
clear oil  The oil was destilled (b p  114-130 °C/ 4 3 x 10$^{-3}$ mbar) Yield  7 40 g (58%)
GCMS  > 99%

¹H-NMR(300 MHz, CDCl₃) δ 9 44 (s, 1H), 7 45 (d, 1H), 7 15 (dd, 1H), 6 90 (d, 1H), 3 89 (s, 3H), 1 43 (s, 6H)

**I-026** 2-Bromo-4-(1,1-dimethyl-allyl)-1-methoxy-benzene

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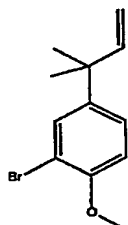


A suspension of methyltriphenylphosphonium bromide (7 71 g, 0 0215 mol) in dry THF (100 mL) was cooled to 0°C under argon n-BuLi (2 5M, 8 mL, 0 020 mol) was added 10 slowly The resulting clear orange solution of the ylide was stirred for another 15 min at 0°C 2-(3-Bromo-4-methoxy-phenyl)-2-methyl-propionaldehyde (3 7 g, 0 014 mol) was dissolved in dry THF (50 mL) and added to ylide-solution The mixture was stirred for 3h/25°C and the resulting suspension was quenched with MeOH (10 mL) The solvent was removed under reduced pressure and the crude product was purified by flash 15 chromatography using n-heptane as eluent Yield 3 1 g (84%) GCMS > 99%
¹H-NMR(300 MHz, CDCl₃) δ 7 50 (d, 1H), 7 23 (dd, 1H), 6 83 (d, 1H), 5 97 (dd, 1H), 5 06 (dd, 1H), 5 02 (dd, 1H), 3 87 (s, 3H), 1 44 (s, 6H)

**I-027** 5-(1,1-Dimethyl-allyl)-2-methoxy-benzaldehyde
20
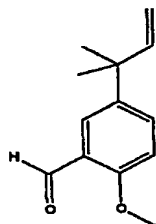


To a solution of 2-Bromo-4-(1,1-dimethyl-allyl)-1-methoxy-benzene (3 1 g, 0 012 mol) in dry THF (50 mL) was cooled to –78°C under argon n-BuLi (2 5M, 5 1 mL, 0 0128 mol) was 25 added keeping the temperature below –70°C The yellow mixture was stirred for another 15 min and quenched with dry DMF (1 4 mL, 0 018 mol) The cooling bath was removed and the mixture was allowed to warm to 25°C A saturated solution of NaHCO₃ (30 mL) was added and then extracted with EtOAc (3 x 50 mL) The organic phase was dried (Na₂SO₄) and evaporated to yellow oil Yield 2 31 g (94%)
30 ¹H-NMR(300 MHz, CDCl₃) δ 10 48 (s, 1H), 7 84 (d, 1H), 7 55 (dd, 1H), 6 94 (d, 1H), 6 00 (dd, 1H), 5 05 (dd, 1H), 5 01 (dd, 1H), 3 93 (s, 3H), 1 41 (s, 6H)

**I-028** 3-[5-Bromo-2-(4-methyl-piperazin-1-yl)-phenyl]-1-(2-fluoro-4-methoxy-phenyl)-propenone
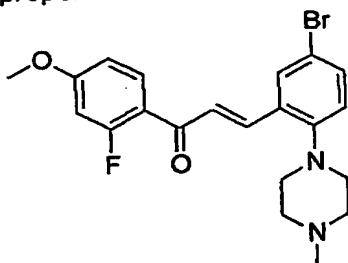


General procedure J gave the title compound as yellow crystals in 65 % yield
$^1$H NMR (CDCl$_3$) δ 8 05 (dd, 1H), 7 91 (t, 1H), 7 76 (d, 1H), 7 46 (dd, 1H), 7 41 (dd, 1H), 6 96 (dd, 1H), 6 82 (dd, 1H), 6 69 (dd, 1H), 3 90 (s, 3H), 3 01 (t, 4H), 2 64 (bs, 4H), 2 39 (s, 3H)

**I-029** 3-(2,4-Dichlorophenyl)-1-(4-fluorophenyl)propan-1-one
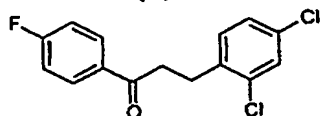


General procedure L gave the title compound as colourless crystals in 53 % yield
$^1$H-NMR(300 MHz, DMSO-d$_6$) δ 8 12-8 04 (m, 2H), 7 58 (d, 1H), 7 46 (d, 1H), 7 40-7 30 (m, 3H), 3 37 (t, 2H), 3 02 (t, 2H)

### References

1) **Synthesis of 2-phenylthiazolidine derivatives as cardiotonic agents I 2-Phenylthiazolidine-3-thiocarboxamides** Nate, Hiroyuki, Sekine, Yasuo, Honma, Yasushi, Nakai, Hideo, Wada, Hiroshi, Takeda, Mikio, Yabana, Hideo, Nagao, Taku Org Chem Res Lab , Tanabe Seiyaku Co , Ltd , Toda, Japan *Chem Pharm Bull* (**1987**), *35(5)*, 1953-68

2) **Preparation of stilbenes as neoplasm inhibitors and agents for treating dermatoses,** EP 331983 A2

3) **Preparation of 5,7-disubstituted-4-aminopyrido[2,3-d]pyrimidines as adenosine kinase inhibitors,** WO 00/23444 A1

**I-030**
(*E*)-3-[3-(2-Dimethylamino-ethylamino)-phenyl]-1-(4-methoxy-phenyl)-propenone
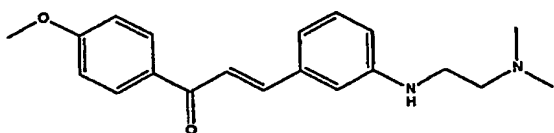
General procedure J gave the fumaric acid salt of title compound as yellow crystals in 64 % yield

5  $^1$H-NMR(300 MHz, DMSO-d$_6$)  δ 8 14 (d, 2H), 7 81 (d, 1H), 7 59 (d, 1H), 7 16 (t, 1H), 7 12-7 00 (m, 4H), 6 73-6 68 (dd, 1H), 6 56 (s, 2H), 3 88 (s, 3H), 3 30 (t, 2H), 2 79 (t, 2H), 2 44 (s, 6H)

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10  **I-031**

(E)-3-(2,4-Dichloro-phenyl)-1-{4-[(2-dimethylamino-ethyl)-methyl-amino]-phenyl}-propenone
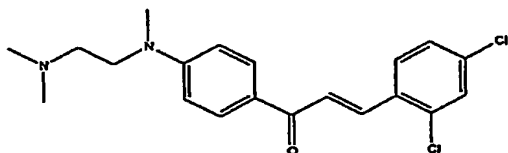
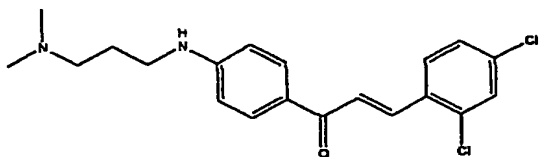15  General procedure J gave the oxalate salt of title compound as yellow crystals in 15 % yield

$^1$H-NMR(300 MHz, DMSO-d$_6$)  δ 8 26 (d, 1H), 8 08 (d, 2H), 8 00 (d, 1H), 7 89 (d, 1H), 7 74 (s, 1H), 7 54 (d, 1H), 6 86 (d, 2H), 3 78 (t, br, 2H), 3 12 (t, br, 2H), 3 07 (s, 3H),
20  2 75 (s, 6H)

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**I-032**

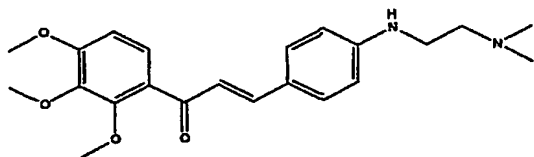(E)-1-{4-[(2-Dimethylamino-ethyl)-methyl-amino]-phenyl}-3-(4-fluoro-phenyl)-
25  propenone
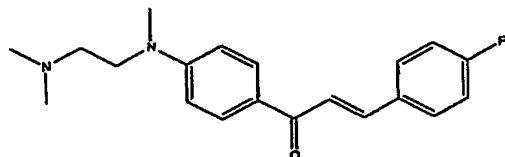
General procedure J gave the oxalate salt of title compound as yellow crystals in 12 % yield

30
$^1$H-NMR(300 MHz, DMSO-d$_6$)  δ 8 06 (d, 2H), 7 98-7 82 (m, 3H), 7 65 (d, 1H), 7 28 (t, 2H), 6 86 (d, 2H), 3 80 (t, 3H), 3 15 (t, 2H), 3 06 (s, 3H), 2 75 (s, 6H)

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## I-033

*(E)*-3-(2,5-Difluoro-phenyl)-1-{4-[(2-dimethylamino-ethyl)-methyl-amino]-phenyl}-propenone
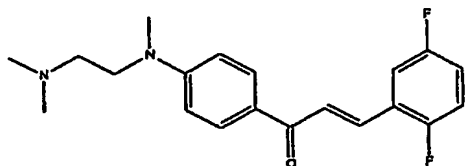
5

General procedure J gave the oxalate salt of title compound as yellow crystals in 12 % yield

$^1$H-NMR(300 MHz, DMSO-$d_6$)  δ 8 11 (m, 4H), 7 69 (d, 1H), 7 41-7 28 (m, 2H), 6 86 (d,
10  2H), 3 80 (t, 3H), 3 15 (t, 2H), 3 06 (s, 3H), 2 75 (s, 6H)

## I-034

*(E)*-3-(2-Bromo-phenyl)-1-{4-[(2-dimethylamino-ethyl)-methyl-amino]-phenyl}-propenone

15

General procedure J gave the oxalate salt of title compound as yellow crystals in 18 % yield

20  $^1$H-NMR(300 MHz, DMSO-$d_6$)  δ 8 16 (dd, 1H), 8 07 (d, 2H), 7 92 (s, 2H), 7 73 (dd, 1H),
7 48 (t, 1H), 7 40-7 36 (td, 1H), 6 86 (d, 2H), 3 79 (t, 3H), 3 11 (t, 2H), 3 04 (s, 3H),
2 74 (s, 6H)

25  ## I-035

*(E)*-3-(4-Bromo-2-fluoro-phenyl)-1-{4-[(2-dimethylamino-ethyl)-methyl-amino]-phenyl}-propenone
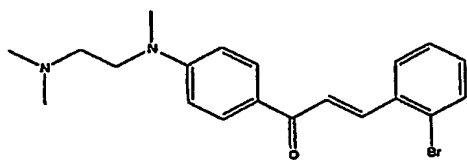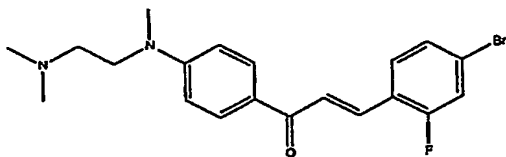
30  General procedure J gave the oxalate salt of title compound as yellow crystals in 18 % yield

$^1$H-NMR(300 MHz, DMSO-$d_6$)  δ 8 12-7 96 (m, 4H), 7 72-7 64 (m, 2H), 7 56-7 50 (dd,
1H), 6 86 (d, 2H), 3 78 (t, 3H), 3 08 (t, 2H), 3 04 (s, 3H), 2 74 (s, 6H)

**I-036**

(*E*)-3-[4-(2-Dimethylamino-ethylamino)-phenyl]-1-(4-methoxy-phenyl)-propenone
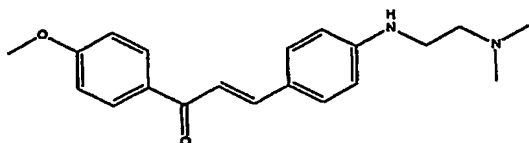


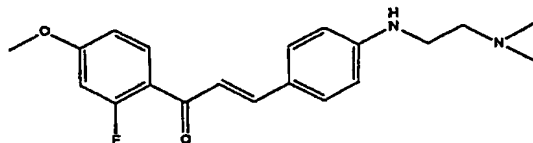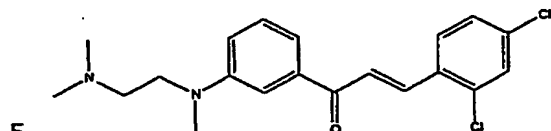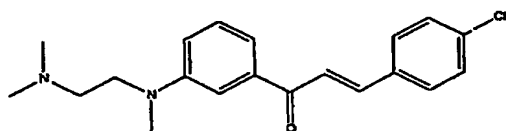General procedure J gave the fumarate salt of title compound as yellow crystals in 44 % yield

¹H-NMR(300 MHz, DMSO-d₆)  δ 8 10 (d, 2H), 7 64-7 58 (m, 4H), 7 05 (d, 2H), 6 65 (d, 2H), 6 58 (d, 2H), 6 38 (s, br, 1H), 3 85 (s, 3H), 2 70 (t, 2H), 2 39(s, 6H)

**I-037**

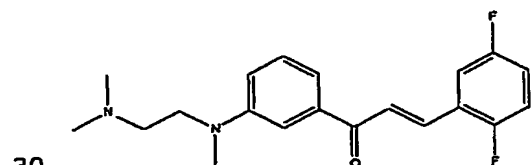(*E*)-3-(4-Chloro-phenyl)-1-{4-[(2-dimethylamino-ethyl)-methyl-amino]-phenyl}-propenone
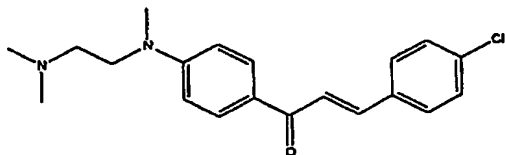


General procedure J gave the oxalate salt of title compound as yellow crystals in 36 % yield

¹H-NMR(300 MHz, DMSO-d₆)  δ 8 07 (d, 2H), 7 97-7 87 (m, 3H), 7 63 (d, 1H), 7 51 (d, 2H), 6 84 (d, 2H), 3 74 (t, 2H), 3 48 (t, 2H), 3 05 (s, 3H), 2 70 (s, 6H)

**I-038**

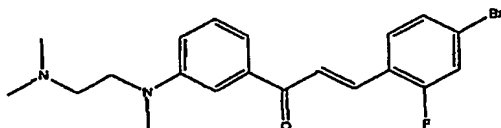(*E*)-3-(3-Bromo-phenyl)-1-{4-[(2-dimethylamino-ethyl)-methyl-amino]-phenyl}-propenone
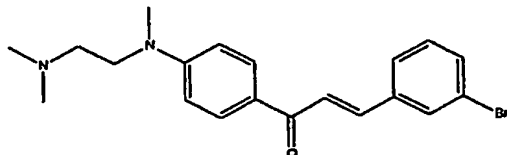


General procedure J gave the oxalate salt of title compound as yellow crystals in 23 % yield

$^1$H-NMR(300 MHz, DMSO-d$_6$) δ 8 17 (s, 1H), 8 09 (d, 2H), 7 95 (d, 1H), 7 83 (d, 1H), 7 65-7 55 (m, 2H), 7 40 (t, 1H), 6 85 (d, 2H), 3 80 (t, 2H), 3 15 (t, 2H), 3 06 (s, 3H), 2 75 (s, 6H)

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### I-039

(E)-4-(3-{4-[(2-Dimethylamino-ethyl)-methyl-amino]-phenyl}-3-oxo-propenyl)-benzonitrile
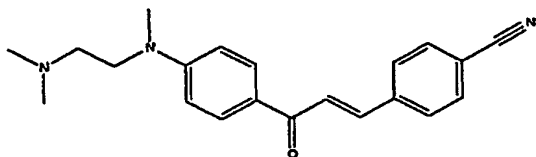


General procedure J gave the oxalate salt of title compound as yellow crystals in 25 % yield

$^1$H-NMR(300 MHz, DMSO-d$_6$) δ 8 12-8 03 (m, 4H), 8 02-7 96 (m, 1H), 7 95-7 88 (m, 2H), 7 67 (d, 1H), 6 85 (d, 2H), 3 75 (t, 2H), 3 10-3 02 (m, 5H), 2 70 (s, 6H)

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### I-040

(E)-3-(2,5-Dimethoxy-phenyl)-1-[4-(3-dimethylamino-propylamino)-phenyl]-propenone
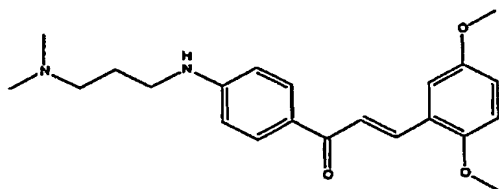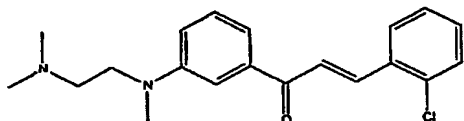


General procedure J gave the oxalate salt of title compound as yellow crystals in 26 % yield

$^1$H-NMR(300 MHz, DMSO-d$_6$) δ 7 98 (d, 2H), 7 92 (d, 1H), 7 83 (d, 1H), 7 49 (d, 1H), 7 06-6 97 (m, 2H), 6 75 (s, br, 1H), 6 66 (d, 2H), 3 84 (s, 3H), 3 79 (s, 3H), 3 20 (t, 2H), 3 09 (t, 2H), 2 74 (s, 6H), 1 92 (m, 2H)

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### I-041

(E)-3-(2,4-Dichloro-phenyl)-1-[4-(3-dimethylamino-propylamino)-phenyl]-propenone
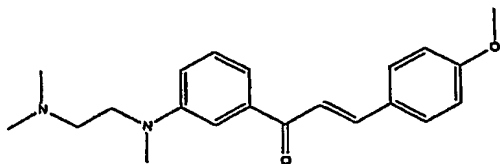
General procedure J gave the oxalate salt of title compound as yellow crystals in 26 % yield

5 ¹H-NMR(300 MHz, DMSO-d₆) δ 8 22 (d, 1H), 8 06-7 92 (m, 3H), 7 86 (d, 1H), 7 72 (d, 1H), 7 52 (dd, 1H), 6 88 (s, br, 1H), 6 67 (d, 2H), 3 22 (t, 2H), 3 10 (t, 2H), 2 74 (s, 6H), 1 93 (m, 2H)

10 **I-042**

(E)-3-[4-(2-Dimethylamino-ethylamino)-phenyl]-1-(2,3,4-trimethoxy-phenyl)-propenone
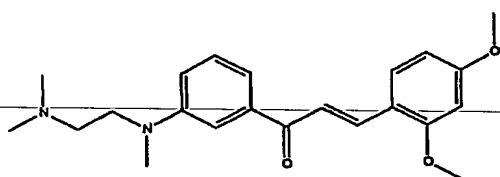


General procedure J gave the fumarate salt of title compound as yellow crystals in 50 %
15 yield

¹H-NMR(300 MHz, DMSO-d₆) δ 7 48 (d, 2H), 7 42 (d, 1H), 7 29 (d, 1H), 7 12 (d, 1H), 6 90 (d, 1H), 6 64 (d, 2H), 6 58 (s, 2H), 6 52 (s, br, 1H), 3 85 (s, 3H), 3 80 (s, 3H), 3 77 (s, 3H), 3 34 (t, 2H), 2 90-2 80 (m, 2H), 2 51 (s, 6H)

20

**I-043**

(E)-3-[4-(2-Dimethylamino-ethylamino)-phenyl]-1-(2-fluoro-4-methoxy-phenyl)-propenone

25
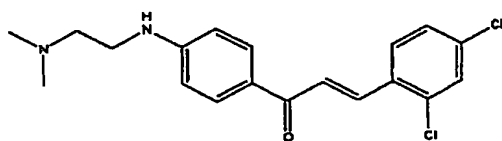


General procedure J gave the fumarate salt of title compound as yellow crystals in 51 %
yield

30 ¹H-NMR(300 MHz, DMSO-d₆) δ 7 78 (t, 1H), 7 58-7 48 (m, 3H), 7 16 (dd, 1H), 6 97-6 87 (m, 2H), 6 64 (d, 2H), 6 58 (s, 2H), 6 41 (s, br, 1H), 3 85 (s, 3H), 3 25 (m, 2H), 2 64 (t, 2H), 2 35 (s, 6H)

**I-044**

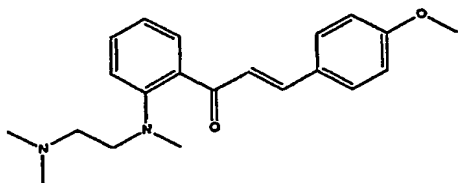(*E*)-3-(2,4-Dichloro-phenyl)-1-{3-[(2-dimethylamino-ethyl)-methyl-amino]-phenyl}-
propenone

5



General procedure J gave the oxalate salt of title compound as yellow crystals in 39 %
yield

10 $^1$H-NMR(300 MHz, DMSO-d$_6$) δ 8 24 (d, 1H), 7 95 (s, 2H), 7 77 (d, 1H), 7 58-7 50 (m,
2H), 7 44-7 34 (m, 2H), 7 12 (dd, 1H), 3 75 (t, 2H), 3 16 (t, 2H), 3 00 (s, 3H), 2 79 (s,
6H)

**I-045**

15 (*E*)-3-(4-Chloro-phenyl)-1-{3-[(2-dimethylamino-ethyl)-methyl-amino]-phenyl}-
propenone



General procedure J gave the oxalate salt of title compound as yellow crystals in 41 %
20 yield

$^1$H-NMR(300 MHz, DMSO-d$_6$) δ 7 94-7 87 (m, 3H), 7 70 (d, 1H), 7 54-7 48 (m, 3H), 7 42-
7 34 (m, 2H), 7 11 (dd, 1H), 3 76 (t, 2H), 3 18 (t, 2H), 3 00 (s, 3H), 2 80 (s, 6H)

25

**I-046**

(*E*)-3-(2,5-Difluoro-phenyl)-1-{3-[(2-dimethylamino-ethyl)-methyl-amino]-phenyl}-
propenone



30

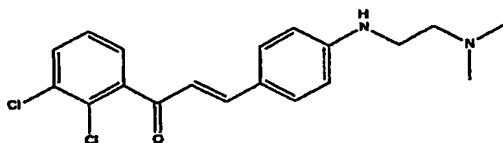General procedure J gave the oxalate salt of title compound as yellow crystals in 15 %
yield

$^1$H-NMR(300 MHz, DMSO-d$_6$) δ 8 10-8 04 (m, 1H), 8 00 (d, 1H), 7 75 (d, 1H), 7 53 (d,
35 1H), 7 44-7 33 (m, 4H), 7 13 (dd, 1H), 3 75 (t, 2H), 3 17 (t, 2H), 3 00 (s, 3H), 2 78 (s,
6H)

**I-047**

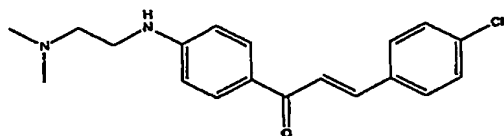(*E*)-3-(4-Bromo-2-fluoro-phenyl)-1-{3-[(2-dimethylamino-ethyl)-methyl-amino]-phenyl}-
5  propenone



General procedure J gave the oxalate salt of title compound as yellow crystals in 35 %
10  yield

$^1$H-NMR(300 MHz, DMSO-d$_6$)  δ 8 09 (t, 1H), 7 96 (d, 1H), 7 73 (d, 1H), 7 69 (dd, 1H),
7 54 (dd, 1H), 7 49 (d, 1H), 7 40 (t, 1H), 7 34 (s, br, 1H), 7 12 (dd, 1H), 3 75 (t, 2H),
3 16 (t, 2H), 3 00 (s, 3H), 2 78 (s, 6H)

15

**I-048**

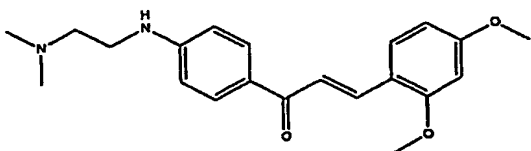(*E*)-3-(2-Chloro-phenyl)-1-{3-[(2-dimethylamino-ethyl)-methyl-amino]-phenyl}-
propenone
20



General procedure J gave the oxalate salt of title compound as yellow crystals in 27 %
yield

25  $^1$H-NMR(300 MHz, DMSO-d$_6$)  δ 8 19 (dd, 1H), 8 02 (d, 1H), 7 92 (d, 1H), 7 57 (dd, 1H),
7 53-7 34 (m, 5H), 7 12 (dd, 1H), 3 75 (t, 2H), 3 15 (t, 2H), 3 00 (s, 3H), 2 78 (s, 6H)

**I-049**

30  (*E*)-1-{3-[(2-Dimethylamino-ethyl)-methyl-amino]-phenyl}-3-(4-methoxy-phenyl)-
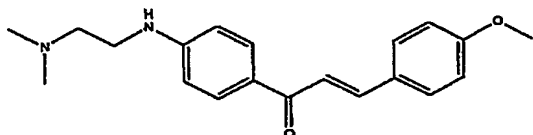propenone

General procedure J gave the oxalate salt of title compound as yellow crystals in 14 % yield

$^1$H-NMR(300 MHz, DMSO-d$_6$) δ 7 84 (d, 2H), 7 73 (d, 1H), 7 68 (d, 1H), 7 47 (d, 1H),
5  7 38 (t, 1H), 7 33 (s, br, 1H), 7 08 (dd, 1H), 7 01 (d, 2H), 3 82 (s, 3H), 3 74 (t, 2H), 3 14 (t, 2H), 2 99 (s, 3H), 2 76 (s, 6H)

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**I-050**
10  (E)-3-(2,4-Dimethoxy-phenyl)-1-{3-[(2-dimethylamino-ethyl)-methyl-amino]-phenyl}-propenone



General procedure J gave the oxalate salt of title compound as yellow crystals in 55 %
15  yield

$^1$H-NMR(300 MHz, DMSO-d$_6$) δ 7 95 (d, 1H), 7 88 (d, 1H), 7 67 (d, 1H), 7 44-7 32 (m, 2H), 7 30 (s, br, 1H), 7 06 (dd, 1H), 6 66-6 58 (m, 2H), 3 58 (s, 3H), 3 65 (s, 3H), 3 54 (t, 2H), 3 12 (t, 2H), 2 97 (s, 3H), 2 75 (s, 6H)

20

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**I-051**
(E)-3-(2,4-Dichloro-phenyl)-1-[4-(2-dimethylamino-ethylamino)-phenyl]-propenone



25
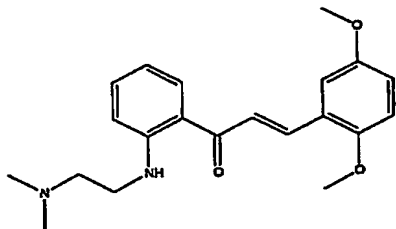
General procedure J gave the fumarate salt of title compound as yellow crystals in 34 %
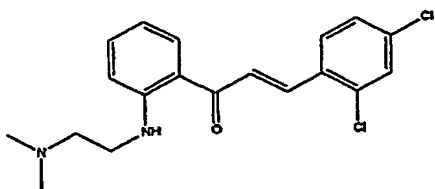yield

$^1$H-NMR(300 MHz, DMSO-d$_6$) δ 8 20 (d, 1H), 8 05-7 91 (m, 3H), 7 86 (d, 1H), 7 71 (d,
30  1H), 7 50 (dd, 1H), 6 88 (s, br, 1H), 6 67 (d, 2H), 3 80 (t, 2H), 3 15 (t, 2H), 3 06 (s, 3H), 2 75 (s, 6H)

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35 **I-052**
(E)-1-{2-[(2-Dimethylamino-ethyl)-methyl-amino]-phenyl}-3-(4-methoxy-phenyl)-propenone

●                                    ●

General procedure J gave the oxalate salt of title compound as yellow crystals in 27 % yield

5

$^1$H-NMR(300 MHz, DMSO-d$_6$) δ 7 72 (d, 2H), 7 54-7 38 (m, 3H), 7 25 (d, 1H), 7 19 (d, 1H), 7 08 (t, 1H), 7 00 (d, 2H), 3 82 (s, 3H), 3 38 (t, 2H), 3 18 (t, 2H), 2 73 (s, 6H), 2 70 (s, 3H)

10

**I-053**

(E)-1-(2,3-Dichloro-phenyl)-3-[4-(2-dimethylamino-ethylamino)-phenyl]-propenone



15  General procedure J gave the fumarate salt of title compound as yellow crystals in 27 % yield

$^1$H-NMR(300 MHz, DMSO-d$_6$) δ 7 76 (dd, 1H), 7 52-7 40 (m, 4H), 7 21 (d, 1H), 6 85 (d, 1H), 6 62 (d, 2H), 6 70 (s, 2H), 3 30-3 22 (m, 2H), 2 65 (t, 2H), 2 35 (s, 6H)

20

**I-054**

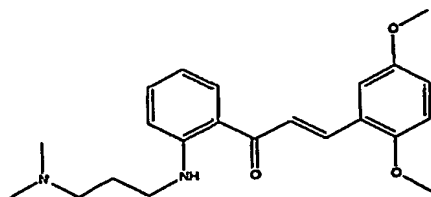(E)-3-(4-Chloro-phenyl)-1-[4-(2-dimethylamino-ethylamino)-phenyl]-propenone



25

General procedure J gave the fumarate salt of title compound as yellow crystals in 28 % yield

$^1$H-NMR(300 MHz, DMSO-d$_6$) δ 7 90 (d, 2H), 7 86 (d, 1H), 7 80 (d, 2H), 7 68 (d, 1H), 30  7 51 (d, 2H), 6 70 (d, 2H), 6 56 (s, 2H), 3 28 (t, 2H), 2 74 (t, 2H), 2 41 (s, 6H)

**I-055**

(E)-3-(2,4-Dimethoxy-phenyl)-1-[4-(2-dimethylamino-ethylamino)-phenyl]-propenone

General procedure J gave the oxalate salt of title compound as yellow crystals in 48 %
yield

$^1$H-NMR(300 MHz, DMSO-d$_6$) δ 7 98 (d, 2H), 7 86 (d, 1H), 7 80 (d, 1H), 7 73 (d, 1H),
7 71 (d, 1H), 7 50 (s, 1H), 6 88 (s, br, 1H), 6 68 (d, 2H), 3 90 (s, 3H), 3 85 (s, 3H), 3 50
(t, 2H), 3 20 (t, 2H), 2 80 (s, 6H)

**I-056**

(*E*)-1-[4-(2-Dimethylamino-ethylamino)-phenyl]-3-(4-methoxy-phenyl)-propenone



General procedure J gave the fumarate salt of title compound as yellow crystals in 45 %
yield

$^1$H-NMR(300 MHz, DMSO-d$_6$) δ 7 98 (d, 2H), 7 86 (d, 1H), 7 82 (d, 2H), 7 73 (d, 1H),
7 00 (d, 2H), 6 88 (s, br, 1H), 6 68 (d, 2H), 6 55 (s, 2H), 3 82 (s, 3H), 3 26 (t, 2H), 2 70
(t, 2H), 2 40 (s, 6H)

**I-057**

(*E*)-3-(2,5-Dimethoxy-phenyl)-1-[2-(2-dimethylamino-ethylamino)-phenyl]-propenone

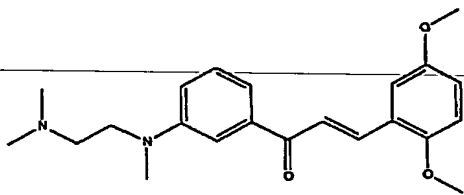

General procedure J gave the oxalate salt of title compound as orange crystals in 61 %
yield

$^1$H-NMR(300 MHz, DMSO-d$_6$) δ 9 11 (t, 1H), 8 20 (d, 1H), 7 95 (s, 2H), 7 52 (d, 1H), 7 47 (t, 1H), 7 08-6 95 (m, 2H), 6 90 (d, 1H), 6 71 (t, 1H), 3 83 (s, 3H), 3 80 (s, 3H), 3 70-3 55 (m, 2H), 3 20 (t, 2H), 2 76 (s, 6H)

5

**I-058**

(*E*)-3-(2,4-Dichloro-phenyl)-1-[2-(2-dimethylamino-ethylamino)-phenyl]-propenone



10   General procedure J gave the oxalate salt of title compound as yellow crystals in 69 % yield

$^1$H-NMR(300 MHz, DMSO-d$_6$) δ 9 13 (t, 1H), 8 24 (t, 2H), 8 08 (d, 1H), 7 90 (d, 1H), 7 72 (d, 1H), 7 56-7 40 (m, 2H), 6 93 (d, 1H), 6 70 (t, 1H), 3 70-3 58 (m, 2H), 3 20 (t, 2H),
15   2 75 (s, 6H)

**I-059**

(*E*)-1-[4-(3-Dimethylamino-propylamino)-phenyl]-3-(4-fluoro-phenyl)-propenone
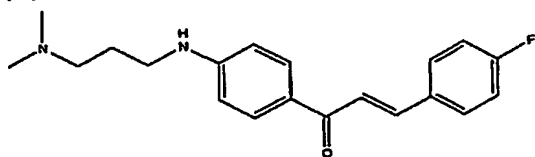


20

General procedure J gave the oxalate salt of title compound as yellow crystals in 64 % yield

$^1$H-NMR(300 MHz, DMSO-d$_6$) δ 7 99 (d, 2H), 7 93 (dd, 2H), 7 84 (d, 1H), 7 62 (d, 1H),
25   7 28 (t, 2H), 6 79 (s, br, 1H), 6 66 (d, 2H), 3 20 (t, 2H), 3 13-3 05 (m, 2H), 2 74 (s, 6H), 2 00-1 85 (m, 2H)

**I-060**

30   (*E*)-3-(2,5-Dimethoxy-phenyl)-1-[2-(3-dimethylamino-propylamino)-phenyl]-propenone

General procedure J gave the oxalate salt of title compound as orange crystals in 71 %
yield

5   $^1$H-NMR(300 MHz, DMSO-d$_6$) δ 9 15 (t, br, 1H), 8 20 (d, 1H), 7 96 (s, 2H), 7 52 (d, 1H),
7 43 (t, 1H), 7 09-6 95 (m, 2H), 6 85 (d, 1H), 6 68 (t, 1H), 3 84 (s, 3H), 3 80 (s, 3H),
3 31 (t, 2H), 3 18-3 01 (m, 2H), 2 74 (s, 6H), 2 05-1 90 (m, 2H)

10  **I-061**
(*E*)-3-(2,5-Dimethoxy-phenyl)-1-{3-[(2-dimethylamino-ethyl)-methyl-amino]-phenyl}-
propenone



15  General procedure J gave the oxalate salt of title compound as yellow crystals in 44 %
yield

$^1$H-NMR(300 MHz, DMSO-d$_6$) δ 7 98 (d, 1H), 7 82 (d, 1H), 7 50 (d, 1H), 7 43-7 30 (m,
2H), 7 27 (t, 1H), 7 08-7 02 (m, 2H), 6 97 (dd, 1H), 3 83 (s, 3H), 3 78 (s, 3H), 3 48 (t,
20  2H), 2 96 (s, 3H), 2 38 (t, 2H), 2 18 (s, 6H)

**I-062**
(*E*)-3-(3-Dibutylamino-phenyl)-1-[2-(3-dimethylamino-propylamino)-phenyl]-propenone
25
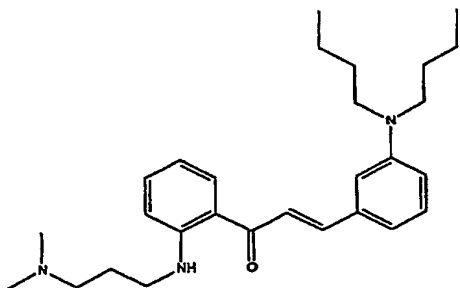


General procedure J gave the title compound as a orange oil in 40 % yield

$^1$H-NMR(300 MHz, DMSO-d$_6$) δ 9 14 (t, 1H), 8 11 (dd, 1H), 7 84 (d, 1H), 7 59 (d, 1H),
30  7 40 (t, 1H), 7 20 (t, 1H), 7 07 (d, 1H), 6 95 (s, 1H), 6 80 (d, 1H), 6 68 (dd, 1H), 6 62 (t,
1H), 3 35-3 20 (m, 6H), 2 32 (t, 2H), 2 15 (s, 6H), 1 80-1 68 (m, 2H), 1 57-1 43 (m, 4H),
1 41-1 25 (m, 4H), 0 92 (t, 6H)

**I-063**

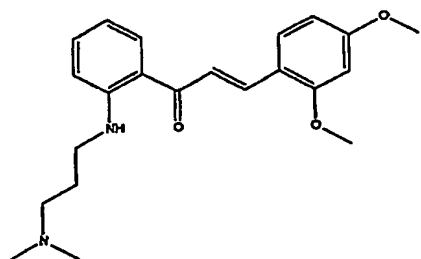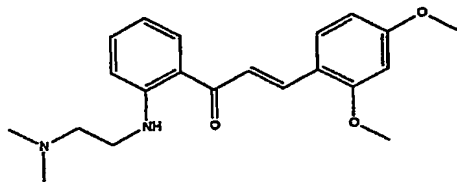(E)-1-[2-(3-Dimethylamino-propylamino)-phenyl]-3-(3-dipropylamino-phenyl)-propenone



5
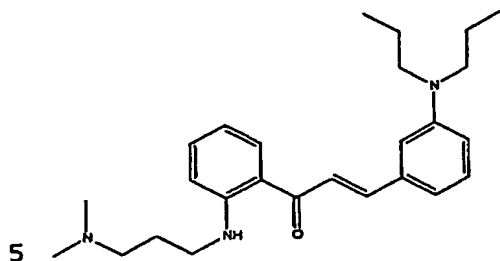
General procedure J gave the title compound as a red oil in 55 % yield

¹H-NMR(300 MHz, DMSO-d₆) δ 9 14 (t, 1H), 8 13 (dd, 1H), 7 85 (d, 1H), 7 60 (d, 1H),

10   7 40 (t, 1H), 7 20 (t, 1H), 7 08 (d, 1H), 6 97 (s, 1H), 6 80 (d, 1H), 6 68 (dd, 1H), 6 62 (t, 1H), 3 35-3 20 (m, 6H), 2 32 (t, 2H), 2 14 (s, 6H), 1 80-1 68 (m, 2H), 1 61-1 45 (m, 4H), 0 90 (t, 6H)

**I-064**

15   (E)-1-[2-(2-Dimethylamino-ethylamino)-phenyl]-3-(3-dipropylamino-phenyl)-propenone
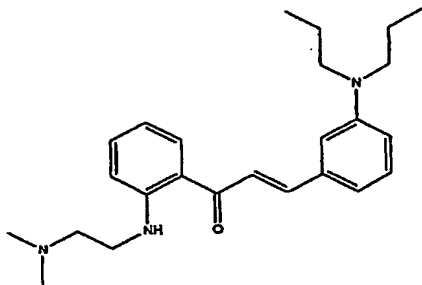


General procedure J gave the title compound as red oil in 54 % yield

20   ¹H-NMR(300 MHz, DMSO-d₆) δ 9 20 (t, 1H), 8 13 (dd, 1H), 7 85 (d, 1H), 7 62 (d, 1H), 7 42 (t, 1H), 7 20 (t, 1H), 7 10 (d, 1H), 6 97 (s, 1H), 6 79 (d, 1H), 6 68 (dd, 1H), 6 63 (t, 1H), 3 35-3 20 (m, 6H), 2 52 (t, 2H), 2 20 (s, 6H), 1 62-1 45 (m, 4H), 0 90 (t, 6H)

25 **I-065**

(E)-3-(2,4-Dimethoxy-phenyl)-1-[2-(3-dimethylamino-propylamino)-phenyl]-propenone

General procedure J gave the fumarate salt of title compound as yellow crystals in 43 % yield

5 $^1$H-NMR(300 MHz, DMSO-d$_6$) δ 9 12 (s, br, 1H), 8 11 (dd, 1H), 7 98-7 75 (m, 3H), 7 40 (td, 1H), 6 81 (d, 1H), 6 70-6 57 (m, 3H), 6 53 (s, 2H), 3 90 (s, 3H), 3 84 (s, 3H), 3 28 (t, 2H), 2 77 (t, 2H), 2 48 (s, 6H), 1 95-1 80 (m, 2H)

10 **I-066**

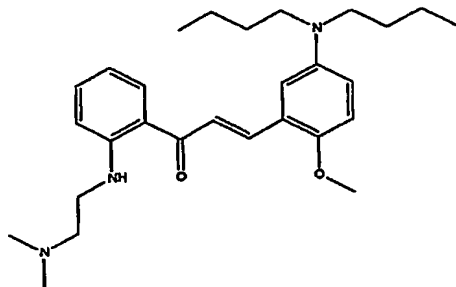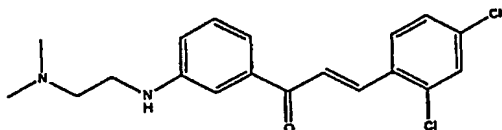(*E*)-3-(2,4-Dimethoxy-phenyl)-1-[2-(2-dimethylamino-ethylamino)-phenyl]-propenone



15 General procedure J gave the fumarate salt of title compound as yellow crystals in 58 % yield

$^1$H-NMR(300 MHz, DMSO-d$_6$) δ 9 13 (t, 1H), 8 10 (dd, 1H), 7 96-7 86 (m, 2H), 7 79 (d, 1H), 7 41 (td, 1H), 6 82 (d, 1H), 6 69-6 60 (m, 3H), 6 58 (s, 2H), 3 90 (s, 3H), 3 85 (s,
20 3H), 3 40-3 30 (m, 2H), 2 82 (t, 2H), 2 38 (s, 6H)

**I-067**

(*E*)-3-(5-Dibutylamino-2-methoxy-phenyl)-1-[2-(2-dimethylamino-ethylamino)-phenyl]-propenone

25

General procedure J gave the title compound as a red oil in 63 % yield

$^1$H-NMR(300 MHz, DMSO-d$_6$)  δ 9 15 (t, 1H), 8 04 (dd, 1H), 7 92 (d, 1H), 7 82 (d, 1H),
7 41 (t, 1H), 7 10 (d, 1H), 6 96 (d, 1H), 6 82-6 72 (m, 2H), 6 63 (t, 1H), 3 80 (s, 3H),
5   3 30-3 18 (m, 6H), 2 53 (t, 2H), 2 21 (s, 6H), 1 55-1 40 (m, 4H), 1 49-1 23 (m, 4H), 0 91
(t, 6H)

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**I-068**
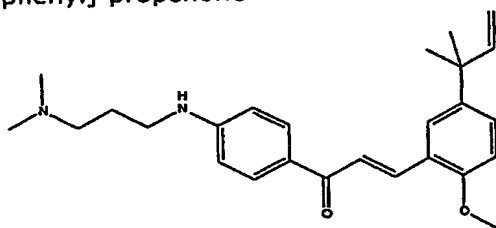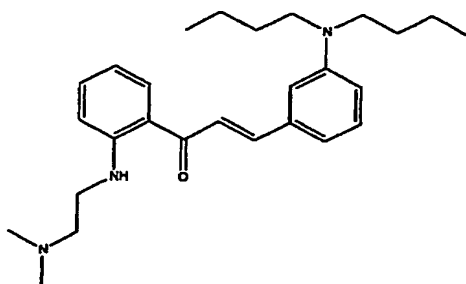10  (E)-3-(2,4-Dichloro-phenyl)-1-[3-(2-dimethylamino-ethylamino)-phenyl]-propenone



General procedure J gave the fumarate salt of title compound as yellow crystals in 56 %
15  yield

$^1$H-NMR(300 MHz, DMSO-d$_6$)  δ 8 21 (d, 1H), 7 91 (s, 2H), 7 75 (d, 1H), 7 54 (dd, 1H),
7 38 (d, 1H), 7 31-7 20 (m, 2H), 6 90 (d, 1H), 6 58 (s, 2H), 5 70 (t, 1H), 3 20-3 10 (m,
2H), 2 45 (t, 2H), 2 18 (s, 6H)

20  ---

**I-069**
(E)-3-[5-(1,1-Dimethyl-allyl)-2-methoxy-phenyl]-1-[4-(3-dimethylamino-propylamino)-
phenyl]-propenone



25
General procedure J gave the fumarate salt of title compound as yellow crystals in 45 %
yield

$^1$H-NMR(300 MHz, DMSO-d$_6$)  δ 8 00-7 82 (m, 3H), 7 79 (d, 2H), 7 33 (d, 1H), 7 01 (d,
30  1H), 6 75 (s, br, 1H), 6 65 (d, 2H), 6 57 (s, 2H), 6 08 (dd, 1H), 5 10-4 94 (m, 2H), 3 85
(s, 3H), 3 18 (t, 2H), 2 65 (t, 2H), 2 39 (s, 6H), 1 88-1 66 (m, 2H), 1 39 (s, 6H)

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**I-070**
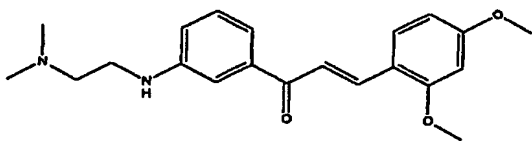35  (E)-3-(3-Dibutylamino-phenyl)-1-[2-(2-dimethylamino-ethylamino)-phenyl]-propenone

47



General procedure J gave the title compound as an orange oil in 54 % yield

5 ¹H-NMR(300 MHz, DMSO-d₆) δ 9 20 (t, 1H), 8 10 (dd, 1H), 7 83 (d, 1H), 7 61 (d, 1H), 7 40 (t, 1H), 7 19 (t, 1H), 7 08 (d, 1H), 6 95 (s, 1H), 6 78 (d, 1H), 6 70-6 56 (m, 2H), 3 35-3 18 (m, 6H), 2 50 (t, 2H), 2 20 (s, 6H), 1 58-1 41 (m, 4H), 1 40-1 25 (m, 4H), 0 92 (t, 6H)

10

**I-071.**

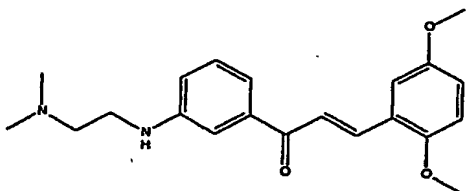(*E*)-3-(2,4-Dimethoxy-phenyl)-1-[3-(2-dimethylamino-ethylamino)-phenyl]-propenone



15

General procedure J gave the oxalate salt of title compound as yellow crystals in 43 % yield

¹H-NMR(300 MHz, DMSO-d₆) δ 7 95 (d, 1H), 7 87 (d, 1H), 7 66 (d, 1H), 7 40-7 20 (m,
20 3H), 6 90 (d, 1H), 6 68-6 59 (m, 2H), 3 90 (s, 3H), 3 85 (s, 3H), 3 47 (t, 2H), 3 21 (t, 2H), 2 79 (s, 6H)

**I-072**
25 (*E*)-3-(2,5-Dimethoxy-phenyl)-1-[3-(2-dimethylamino-ethylamino)-phenyl]-propenone



General procedure J gave the oxalate salt of title compound as yellow crystals in 27 % yield
30

$^1$H-NMR(300 MHz, DMSO-d$_6$) δ 7 73 (d, 1H), 7 55 (d, 1H), 7 26 (s, 1H), 7 18 (d, 1H), 7 07 (t, 1H), 7 01 (s, 1H), 6 80 (s, 2H), 6 68 (d, 1H), 3 58 (s, 3H), 3 52 (s, 3H), 3 20 (t, 2H), 2 95 (t, 2H), 2 79 (s, 6H)

5

**I-073**
(*E*)-3-(2,4-Dimethoxy-phenyl)-1-{2-[(2-dimethylamino-ethyl)-methyl-amino]-phenyl}-propenone
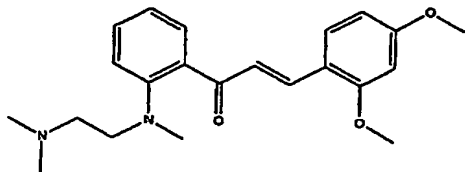


10

General procedure J gave the title compound as yellow oil in 36 % yield
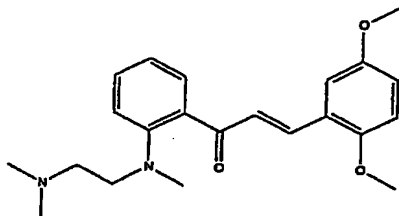
$^1$H-NMR(300 MHz, DMSO-d$_6$) δ 7 80 (d, 1H), 7 68 (d, 1H), 7 45-7 27 (m, 3H), 7 13 (d, 1H), 6 95 (t, 1H), 6 65-6 57 (m, 2H), 3 86 (s, 3H), 3 82 (s, 3H), 3 12 (t, 2H), 2 74 (s, 3H), 2 35 (t, 2H), 2 06 (s, 6H)

15

**I-074**
(*E*)-3-(2,5-Dimethoxy-phenyl)-1-{2-[(2-dimethylamino-ethyl)-methyl-amino]-phenyl}-propenone

20



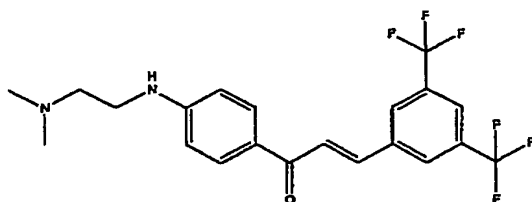General procedure J gave the title compound as a red oil in 83 % yield

25 $^1$H-NMR(300 MHz, DMSO-d$_6$) δ 7 83 (d, 1H), 7 48-7 36 (m, 3H), 7 27 (d, 1H), 7 15 (1H), 7 06-6 92 (m, 3H), 3 80 (s, 3H), 3 73 (s, 3H), 3 11 (t, 2H), 2 74 (s, 3H), 2 36 (t, 2H), 2 06 (s, 6H)

30 **I-075**
(*E*)-3-(3,5-Bis-trifluoromethyl-phenyl)-1-[4-(2-dimethylamino-ethylamino)-phenyl]-propenone
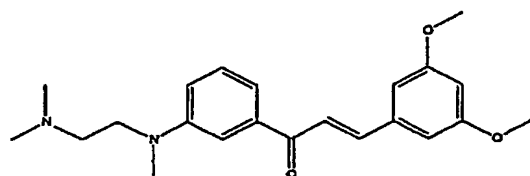
● ●

General procedure J gave the title compound as yellow solid in 36 % yield

5   ¹H-NMR(300 MHz, DMSO-d₆)  δ 8 10 (s, 2H), 7 95 (d, 2H), 7 88 (s, 1H), 7 77 (d, 1H), 7 67 (d, 1H), 6 66 (d, 2H), 5 08 (t, br, 1H), 3 30-3 18 (m, 2H), 2 59 (t, 2H), 2 27 (s, 6H)

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**I-076**

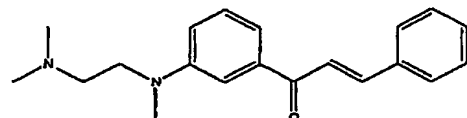10  (E)-3-(3,5-Dimethoxy-phenyl)-1-{3-[(2-dimethylamino-ethyl)-methyl-amino]-phenyl}-propenone



General procedure J gave the fumarate salt of title compound as yellow crystals in 32 %

15  yield

¹H-NMR(300 MHz, DMSO-d₆)  δ 7 88 (d, 1H), 7 65 (d, 1H), 7 49 (d, 1H), 7 40-7 26 (m, 2H), 7 10-6 92 (m, 3H), 6 58 (d, 2H), 3 80 (s, 6H), 3 61 (t, 2H), 2 62 (t, 2H), 2 39 (s, 6H)

20

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**I-077**

(E)-1-{3-[(2-Dimethylamino-ethyl)-methyl-amino]-phenyl}-3-phenyl-propenone
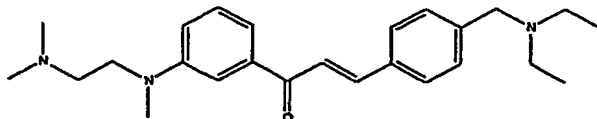


25

General procedure J gave the fumarate salt of title compound as yellow crystals in 28 % yield

¹H-NMR(300 MHz, DMSO-d₆)  δ 7 92-7 83 (m, 3H), 7 72 (d, 1H), 7 50-7 43 (m, 4H), 7 40-
30  7 30 (m, 2H), 7 08-7 02 (dd, 1H), 6 58 (s, 2H), 3 62 (t, 2H), 2 95 (s, 3H), 2 73 (t, 2H), 2 45 (s, 6H)

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**I-078**

(E)-3-(4-Diethylaminomethyl-phenyl)-1-{3-[(2-dimethylamino-ethyl)-methyl-amino]-phenyl}-propenone

5

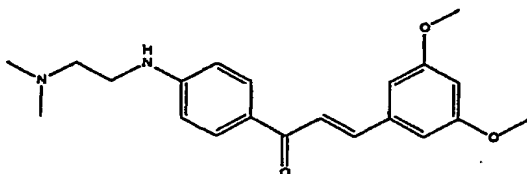General procedure J gave the title compound as yellow oil in 25 % yield

¹H-NMR(300 MHz, CDCl₃) δ 7 93 (d, 1H), 7 72 (d, 2H), 7 63 (d, 1H), 7 58-7 41 (m, 5H), 7 40 (s, 2H), 7 10-7 04 (m, 1H), 3 72 (s, 2H), 3 65 (t, 2H), 3 16 (s, 3H), 2 73-2 60 (m,
10  6H), 2 45 (s, 6H), 1 19 (t, 6H)

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**I-079**

(E)-3-(3,5-Dimethoxy-phenyl)-1-[4-(2-dimethylamino-ethylamino)-phenyl]-propenone
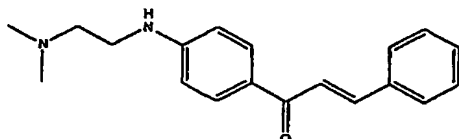
15

General procedure J gave the fumarate salt of title compound as yellow crystals in 50 % yield

20  ¹H-NMR(300 MHz, DMSO-d₆) δ 8 00 (d, 2H), 7 88 (d, 1H), 7 54 (d, 1H), 7 00 (s, 2H), 6 68 (d, 3H), 6 55 (s, 2H), 3 80 (s, 6H), 3 35-3 20 (m, 2H), 2 65 (t, 2H), 2 35 (s, 3H)

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**I-080**

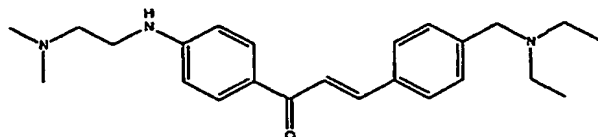25  (E)-1-[4-(2-Dimethylamino-ethylamino)-phenyl]-3-phenyl-propenone

General procedure J gave the fumarate salt of title compound as yellow crystals in 45 % yield

30

¹H-NMR(300 MHz, DMSO-d₆) δ 7 98 (d, 2H), 7 94-7 80 (m, 3H), 7 62 (d, 1H), 7 50-7 38 (m, 3H), 6 75-6 65 (m, 3H), 6 57 (s, 2H), 3 31 (q, 2H), 2 67 (t, 2H), 2 36 (s, 6H)

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51

## I-081
(*E*)-3-[4-Diethylaminomethyl-phenyl)-1-[4-(2-dimethylamino-ethylamino)-phenyl]-propenone

5



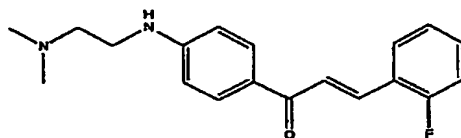General procedure J gave the title compound as yellow oil in 36 % yield

¹H-NMR(300 MHz, CDCl₃) δ 7 98 (d, 2H), 7 90 (d, 1H), 7 63-7 52 (m, 3H), 7 39 (d, 2H),
6 64 (d, 2H), 4 95 (t, 1H), 3 60 (s, 2H), 3 23 (q, 2H), 2 60-2 48 (m, 6H), 2 29 (s, 6H),
10  1 06 (t, 6H)

## I-082
(*E*)-1-[4-(2-Dimethylamino-ethylamino)-phenyl]-3-(2-fluoro-phenyl)-propenone

15



General procedure J gave the fumarate salt of title compound as yellow crystals in 50 %
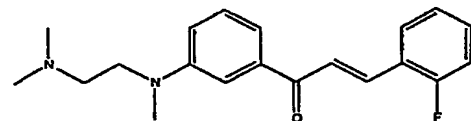yield

20

¹H-NMR(300 MHz, DMSO-d₆) δ 8 08 (t, 1H), 8 02-7 88 (m, 3H), 7 74 (d, 1H), 7 54-7 43
(m, 1H), 7 37-7 25 (m, 2H), 6 76 (t, 1H), 6 68 (d, 2H), 6 57 (s, 2H), 3 32 (q, 2H), 2 66 (t,
2H), 2 35 (s, 6H)

25

## I-083
(*E*)-1-{3-[(2-Dimethylamino-ethyl)-methyl-amino]-phenyl}-3-(2-fluoro-phenyl)-propenone



30

General procedure J gave the oxalate salt of title compound as yellow crystals in 26 %
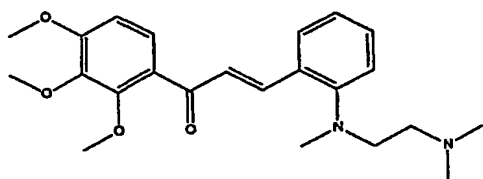yield

35  ¹H-NMR(300 MHz, DMSO-d₆) δ 8 12 (t, 1H), 7 94 (d, 1H), 7 82 (d, 1H), 7 58-7 47 (m,
2H), 7 45-7 28 (m, 4H), 7 13 (dd, 1H), 3 78 (t, 2H), 3 22 (t, 2H), 3 00 (s, 3H), 2 82 (s,

6H)

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**I-084**

5  (*E*)-3-{2-[(2-Dimethylamino-ethyl)-methyl-amino]-phenyl}-1-(2,3,4-trimethoxy-phenyl)-
propenone



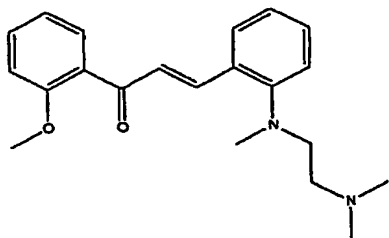General procedure J gave the title compound as yellow oil in 41 % yield

10

$^1$H-NMR(300 MHz, CDCl$_3$)  δ 8 06 (d, 1H), 7 65 (dd, 1H), 7 48 (d, 1H), 7 43 (d, 1H), 7 34
(td, 1H), 7 11 (d, 1H), 7 04 (t, 1H), 6 77 (d, 1H), 3 97 (s, 3H), 3 95 (s, 3H), 3 94 (s, 3H),
3 10 (m, 2H), 2 80 (s, 3H), 2 52 (m, 2H), 2 22 (s, 6H)

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15

**I-085.**
(*E*)-3-{2-[(2-Dimethylamino-ethyl)-methyl-amino]-phenyl}-1-(2-methoxy-phenyl)-
propenone



20

General procedure J gave the title compound as yellow oil in 37 % yield

$^1$H-NMR(300 MHz, DMSO-d$_6$)  δ 7 73 (d, 1H), 7 69 (dd, 1H), 7 53 (td, 1H), 7 46 (dd, 1H),
25  7 37 (td, 1H), 7 25 (d, 1H), 7 18 (d, 1H), 7 14 (d, 1H), 7 10-7 01 (m, 2H), 3 84 (s, 3H),
2 95 (t, 2H), 2 70 (s, 3H), 2 33 (t, 2H), 2 05 (s, 6H)

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**I-086**
30  (*E*)-3-{2-[(2-Dimethylamino-ethyl)-methyl-amino]-phenyl}-1-(2-dimethylaminomethyl-
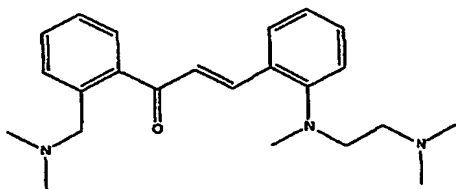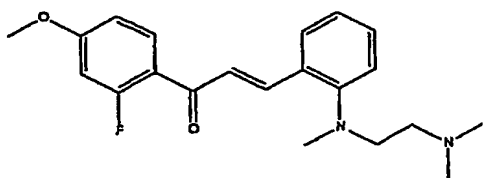phenyl)-
propenone

General procedure J gave the title compound as yellow oil in 58 % yield

5  ¹H-NMR(300 MHz, CDCl₃)  δ 7 67 (d, 1H), 7 62 (dd, 1H), 7 46-7 30 (m, 5H), 7 13-7 03 (m, 3H), 3 56 (s, 2H), 3 03 (t, 2H), 2 71 (s, 3H), 2 35 (t, 2H), 2 17 (s, 12H)

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**I-087**

10  (E)-3-{2-[(2-Dimethylamino-ethyl)-methyl-amino]-phenyl}-1-(2-fluoro-4-methoxy-phenyl)-propenone
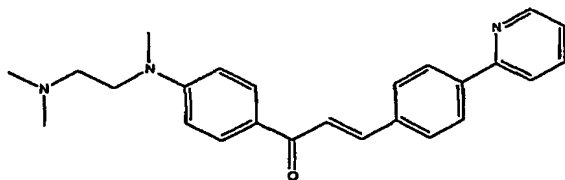


General procedure J gave the fumarate salt of title compound as yellow crystals in 41 %
15  yield

¹H-NMR(300 MHz, DMSO-d₆)  δ 7 92 (d, 1H), 7 83 (t, 1H), 7 76 (dd, 1H), 7 47-7 37 (m, 2H), 7 21 (d, 1H), 7 10 (t, 1H), 7 02-6 90 (m, 2H), 6 57 (s, 2H), 3 86 (s, 3H), 3 10 (t, 2H), 2 77-2 61 (m, 5H), 2 29 (s, 6H)

20

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**I-088:**

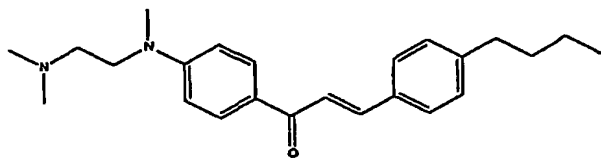(E)-1-{4-[(2-Dimethylamino-ethyl)-methyl-amino]-phenyl}-3-(4-pyridin-2-yl-phenyl)-propenone

25



General procedure J gave the title compound as a yellow solid in 35 % yield

¹H-NMR(300 MHz, CDCl₃)  δ 8 73 (d, 1H), 8 09-8 02 (m, 4H), 7 87-7 75 (m, 5H), 7 66 (d,
30  1H), 7 31-7 24 (m, 1H), 6 74 (d, 2H), 3 57 (t, 2H), 3 10, (s, 3H), 2 54 (t, 2H), 2 30 (s, 6H)

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**I-089**
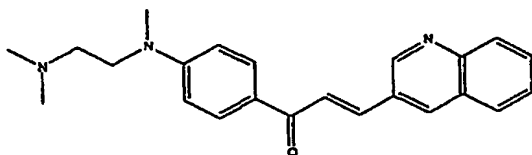(E)-3-(4-Butyl-phenyl)-1-{4-[(2-dimethylamino-ethyl)-methyl-amino]-phenyl}-propenone



5  General procedure J gave the fumarate salt of title compound as yellow crystals in 30 % yield

$^1$H-NMR(300 MHz, DMSO-d$_6$) δ 8 04 (d, 2H), 7 85 (d, 1H), 7 75 (d, 2H), 7 62 (d, 1H),
10  7 27 (d, 2H), 6 79 (d, 2H), 6 59 (s, 2H), 3 64 (t, 2H), 3 04, (s, 3H), 2 70-2 59 (m, 4H), 2 39 (s, 6H), 1 60-1 55 (m, 2H), 1 35-1 27 (m, 2H), 0 90 (t, 3H)

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**I-090**
15  (E)-1-{4-[(2-Dimethylamino-ethyl)-methyl-amino]-phenyl}-3-quinolin-3-yl-propenone



General procedure J gave the fumarate salt of title compound as yellow crystals in 46 % yield

20  $^1$H-NMR(300 MHz, DMSO-d$_6$) δ 9 43 (d, 1H), 8 80 (d, 1H), 8 22 (d, 1H), 8 13-8 00 (m, 4H), 7,86-7 78 (m, 2H), 7 67 (dd, 1H), 6 83 (d, 2H), 6 60 (s, 3H), 3 67 (t, 2H), 3 06, (s, 3H), 2 71 (t, 2H), 2 42 (s, 6H)

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25  **I-091**
(E)-1-[4-(2-Dimethylamino-ethylamino)-phenyl]-3-(4-pyridin-2-yl-phenyl)-propenone
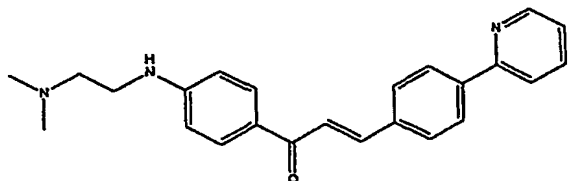


30  General procedure J gave the fumarate salt of title compound as yellow crystals in 36 % yield

$^1$H-NMR(300 MHz, DMSO-d$_6$) δ 8 70 (d, 1H), 8 18 (d, 2H), 8 08-7 88 (m, 7H), 7,68 (d, 1H), 7 39 (ddd, 1H), 6 69 (d, 1H), 6 65 (t, 1H), 6 57 (s, 1H), 3 28, (q, 2H), 2 58 (t, 2H), 2 29 (s, 6H)

**I-092.**
(*E*)-3-(4-Butyl-phenyl)-1-[4-(2-dimethylamino-ethylamino)-phenyl]-propenone

General procedure J gave the fumarate salt of title compound as yellow crystals in 35 % yield

$^1$H-NMR(300 MHz, DMSO-d$_6$) δ 7 83 (d, 2H), 7 69 (d, 1H), 7 61 (d, 2H), 7,46 (d, 1H), 7 13 (d, 2H), 6 54 (d, 2H), 6 48 (d, 1H), 6 43 (s, 1H), 3 12, (q, 2H), 2 51-2 42 (m, 4H), 2 16 (s, 6H), 1 46-1 41 (m, 2H), 1 22-1 14 (m, 2H), 0 77 (t, 3H)

**I-093**
(*E*)-1-[4-(2-Dimethylamino-ethylamino)-phenyl]-3-(4-methoxy-biphenyl-3-yl)-propenone

General procedure J gave the fumarate salt of title compound as yellow crystals in 28 % yield

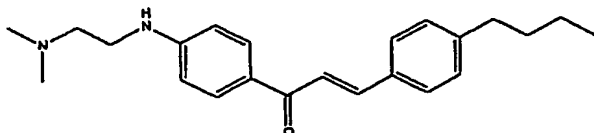$^1$H-NMR(300 MHz, DMSO-d$_6$) δ 8 22 (d, 1H), 8 02-7 99 (m, 4H), 7 78-7 74 (m, 2H), 7,71 (d, 1H), 7 48 (dd, 2H), 7 36 (dd, 1H), 7 20 (d, 1H), 6 68 (d, 2H), 6 63 (t, 1H), 6 59 (s, 2H), 3 94 (s, 3H), 3 27, (q, 2H), 2 60 (t, 2H), 2 31 (s, 6H)

**I-094**
(*E*)-3-{3-[(2-Dimethylamino-ethyl)-methyl-amino]-phenyl}-1-[2-(4-methyl-piperazin-1-ylmethyl)-phenyl]-propenone
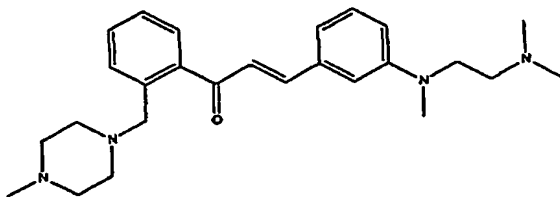
General procedure J gave the title compound as an orange oil in 33 % yield

5  ¹H-NMR(300 MHz, CDCl₃)  δ 7 44-7 32 (m, 4H), 7 24 (t, 1H), 7 18 (d, 1H), 7 00 (d, 1H), 6 88 (d, 1H), 6 82-6 73 (m, 2H), 3 60 (s, 2H), 3 48 (t, 2H), 2 98 (s, 3H), 2 49 (t, 2H), 2 48-2 34 (br, 8H), 2 30 (s, 6H), 2 20 (s, 3H)

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10  **I-095**

(E)-1-[4-(2-Dimethylamino-ethylamino)-phenyl]-3-quinolin-3-yl-propenone
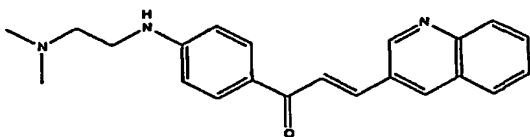


General procedure J gave the title compound as yellow solid in 37 % yield

15
¹H-NMR(300 MHz, CDCl₃)  δ 9 23 (d, 1H), 8 34 (d, 1H), 8 14 (d, 1H), 8 03 (d, 2H), 7 95 (d, 1H), 7 89 (d, 1H), 7,81 (d, 1H), 7 79-7 74 (m, 1H), 7 61 (dd, 1H) 6 67 (d, 2H), 5 04 (t, 1H), 3 26, (dt, 2H), 2 61 (d, 2H), 2 29 (s, 6H)

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20
**I-096**

(E)-1-[4-(2-Dimethylamino-ethylamino)-phenyl]-3-quinolin-2-yl-propenone



25
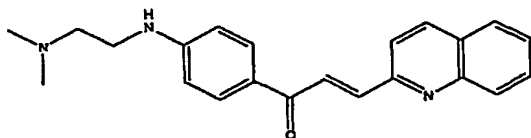
General procedure J gave the title compound as yellow solid in 17 % yield

¹H-NMR(300 MHz, CDCl₃)  8 17-8 06 (m, 3H), 8 00 (d, 2H), 7 86 (d, 1H), 7 76 (d, 1H), 7 68 (dd, 1H), 7,59 (d, 1H), 7 49 (dd, 1H), 6 58 (d, 2H), 4 94 (t, 1H), 3 17, (dt, 2H), 2 52

30  (d, 2H), 2 20 (s, 6H)

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**I-097**

(E)-1-[4-(2-Dimethylamino-ethylamino)-phenyl]-3-(4-dimethylamino-phenyl)-propenone

57
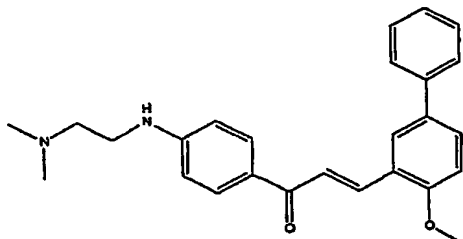


General procedure J gave the fumarate salt of title compound as yellow crystals in 20 % yield

5

$^1$H-NMR(300 MHz, DMSO-d$_6$) δ 8 06 (d, 2H), 7 78 (d, 2H), 7,70 (d, 2H), 6 86 (d, 2H), 6 78 (d, 2H), 6 70 (s, 2H), 6 65 (t, 1H), 3 39 (dt, 2H), 3 12 (s, 6H), 2 75 (t, 2H), 2 45 (s, 6H)

10

**I-098**
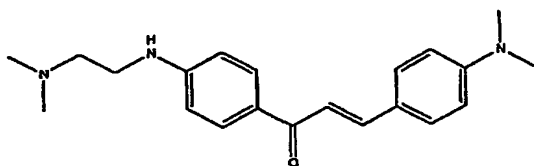(E)-1-[4-(2-Dimethylamino-ethylamino)-phenyl]-3-(4-imidazol-1-yl-phenyl)-propenone



15  General procedure J gave the title compound as orange solid in 34 % yield

$^1$H-NMR(300 MHz, CDCl$_3$) δ 7 99 (d, 2H), 7,93 (t, 1H), 7 83-7 75 (m, 3H), 7 60 (d, 1H), 7 47 (d, 2H), 7 34 (t, 1H), 7 25 (t, 1H), 6 66 (d, 2H), 5 01 (t, 1H), 3 25, (dt, 2H), 2 60 (d, 2H), 2 29 (s, 6H)

20

**I-099**
(E)-3-(2,3-Dihydro-benzo[1,4]dioxin-6-yl)-1-[4-(2-dimethylamino-ethylamino)-phenyl]-propenone

25



General procedure J gave the fumarate salt of title compound as yellow crystals in 13 % yield

30  $^1$H-NMR(300 MHz, DMSO-d$_6$) δ 7 97 (d, 2H), 7 74 (d, 1H), 7,52 (d, 1H), 7 43 (d, 1H), 7 31 (dd, 1H), 6 90 (d, 1H), 6 70-6 65 (m, 3H), 6 58 (s, 2H), 4 29 (bs, 4H), 3 34 (dt, 2H), 2 75 (t, 2H), 2 42 (s, 6H)

### I-100

(*E*)-1-[4-(2-Dimethylamino-ethylamino)-phenyl]-3-{3-[(2-dimethylamino-ethyl)-methyl-amino]-phenyl}-propenone



General procedure J gave the fumarate salt of title compound as yellow crystals in 15 % yield

$^1$H-NMR(300 MHz, DMSO-d$_6$) δ 7 97 (d, 2H), 7 80 (d, 1H), 7,57 (d, 1H), 7 23 (dd, 1H), 7 12-7 09 (m, 2H), 6 77 (dd, 1H), 6 68 (d, 2H), 6 62 (t, 1H), 6 57 (s, 2H), 3 54 (t, 1H), 3 28 (dt, 2H), 2 96 (s, 3H), 2 62-2-57 (m, 4H), 2 30 (s, 6H), 2 09 (s, 6H)

### I-101

(*E*)-1-[4-(2-Dimethylamino-ethylamino)-phenyl]-3-(2-dimethylaminomethyl-phenyl)-propenone



General procedure J gave the title compound as yellow solid in 10 % yield

$^1$H-NMR(300 MHz, CDCl$_3$) δ 8 24 (d, 1H), 8 00 (d, 2H), 7 76-7 73 (m, 1H), 7 70 (d, 1H), 7 37-7 32 (m, 3H), 6 65 (d, 1H), 4 95 (t, 1H), 3 57 (s, 2H), 3 25 (dt, 2H), 2 60 (t, 2H), 2 29 (s, 6H), 2 28 (s, 6H)

### I-102·

(*E*)-1-{4-[(2-Dimethylamino-ethyl)-methyl-amino]-phenyl}-3-(4-methoxy-biphenyl-3-yl)-propenone



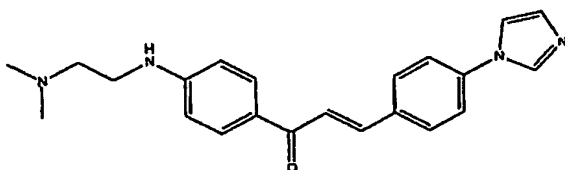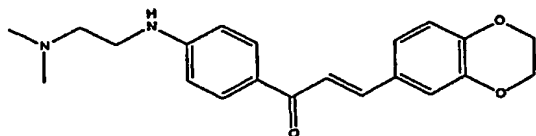General procedure J gave the fumarate salt of title compound as yellow crystals in 36 % yield

¹H-NMR(300 MHz, DMSO-d₆) δ 8 23 (d, 1H), 8 07 (d, 2H), 8 02 (s, 2H), 7 78-7 71 (m, 3H), 7 48 (dd, 2H), 7,35 (d, 1H), 7 20 (d, 1H), 6 80 (d, 1H), 6 59 (s, 2H), 3 94 (s, 3H), 3 65 (t, 1H), 3 04, (s, 3H), 2 69 (t, 2H), 2 40 (s, 6H)

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**I-103**
(E)-3-{3-[(2-Dimethylamino-ethyl)-methyl-amino]-phenyl}-1-(2-dimethylaminomethyl-phenyl)-propenone



10
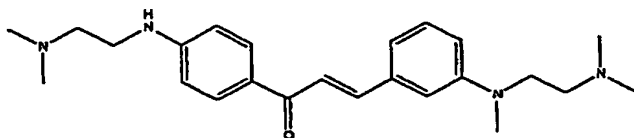
General procedure J gave the fumarate salt of title compound as yellow crystals in 42 % yield

15 ¹H-NMR(300 MHz, DMSO-d₆) δ 7 54-7 38 (m, 4H), 7 27 (s, 2H), 7 22 (t, 1H), 7 05-6 98 (m, 2H), 6 81 (dd, 1H), 6 58 (s, 4H), 3 61 (s, 2H), 3 59 (t, 2H), 2 93 (s, 3H), 2 78 (t, 2H), 2 48 (s, 6H), 2 13 (s, 6H)

20 **I-104·**
(E)-3-[4-(2-Dimethylamino-ethoxy)-biphenyl-3-yl]-1-[4-(2-dimethylamino-ethylamino)-phenyl]-propenone
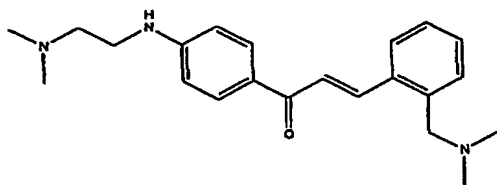


25

General procedure J gave the fumarate salt of title compound as yellow crystals in 14 % yield

$^1$H-NMR(300 MHz, DMSO-d$_6$) δ 8 16 (d, 1H), 8 08 (d, 1H), 8 01 (d, 2H), 7 96 (d, 1H), 7 75 (d, 2H), 7,70 (dd, 1H), 7 47 (dd, 2H), 7 35 (dd, 1H), 7 23 (d, 1H), 6 69 (d, 2H), 6 58 (s, 2H), 4 28 (t, 1H), 3 32 (dt, 2H), 2 89 (t, 2H), 2 70 (t, 2H), 2 38 (s, 6H)

5

### I-105

1-[4-(2-Dimethylamino-ethylamino)-phenyl]-3-(2-dimethylaminomethyl-phenyl)-propenone



10
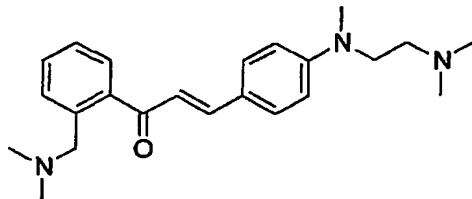
General procedure J gave the fumarate salt of title compound as orange crystals in 38 % yield

$^1$H-NMR(300 MHz, DMSO-d$_6$) δ 7 6-7 4 (m, 6H), 7 26 (d, 1H), 7 17 (d, 1H), 6 74 (d, 2H), 15   6 58 (s, 4H), 3 65 (s, 2H), 3 59 (t, 2H), 2 98 (s, 3H), 2 67 (t, 2H), 2 40 (s, 6H), 2 19 (s, 6H)

### I-106

20   (E)-3-{2-[(2-Dimethylamino-ethyl)-methyl-amino]-phenyl}-1-[2-(4-methyl-piperazin-1-ylmethyl)-phenyl]-propenone
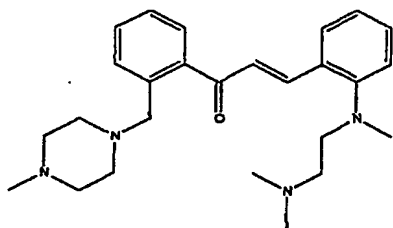


General procedure J gave the fumarate salt of title compound as yellow crystals in 59 % 25   yield

$^1$H-NMR(300 MHz, DMSO-d$_6$) δ 7 78 (dd, 1H), 7 54 (d, 1H), 7 50-7 33 (m, 5H), 7 18 (d, 1H), 7 14-7 05 (m, 2H), 6 57 (s, 4H), 3 55 (s, 2H), 3 04 (t, 2H), 2 63 (s, 3H), 2 54 (t, 2H), 2 42-2 25 (br, 8H), 2 24 (s, 6H), 2 18 (s, 3H)

30

### I-107

(E)-1-{4-[(2-Dimethylamino-ethyl)-methyl-amino]-phenyl}-3-(2-dimethylaminomethyl-phenyl)-propenone
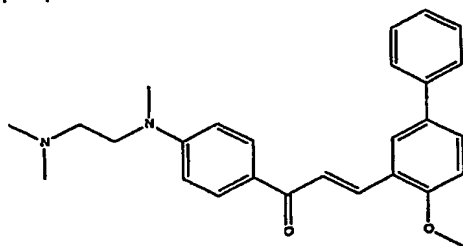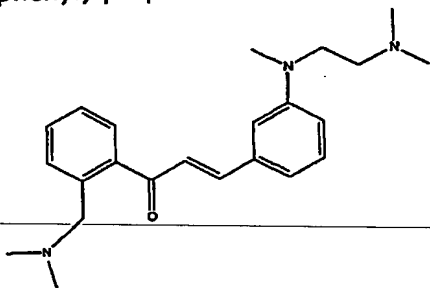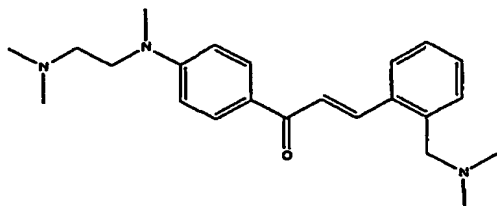
General procedure J gave the title compound as yellow oil in 33% yield

5   $^1$H-NMR(300 MHz, CDCl$_3$)  δ 8 23 (d, 1H), 8 01 (d, 2H), 7 74-7 71 (m, 1H), 7 50 (d, 1H), 7 35-7 29 (m, 3H), 6 70 (d, 1H), 3 57-3 52 (m, 4H), 3 07 (s, 3H), 2 51 (t, 2H), 2 30 (s, 6H), 2 26 (s, 6H)

10  **I-108**

(*E*)-1-{4-[(2-Dimethylamino-ethyl)-methyl-amino]-phenyl}-3-(4-imidazol-1-yl-phenyl)-propenone
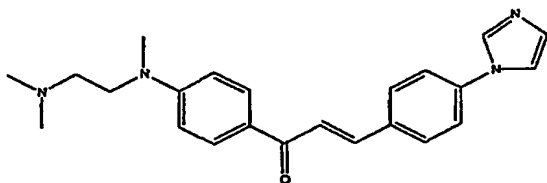


15  General procedure J gave the title compound as pale brown solid in 23 % yield

$^1$H-NMR(300 MHz, CDCl$_3$)  δ 8 00 (d, 2H), 7 90 (t, 1H), 7 77 (d, 1H), 7 73 (d, 2H), 7 59 (d, 1H), 7 42 (d, 2H), 7 31 (t, 1H), 7 22 (t, 1H), 6 71 (d, 2H), 3 54 (t, 2H), 3 07, (s, 3H), 2 47 (t, 2H), 2 29 (s, 6H)

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**I-109**

1-[4-(2-Dimethylamino-ethylamino)-phenyl]-3-(4-phenoxy-phenyl)-propenone



25
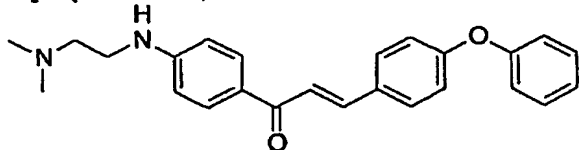
General procedure J gave the title compound as yellow crystals in 39 % yield

$^1$H NMR (CDCl$_3$)  δ 7 98 (d, 2H), 7 78 (d, 1H), 7 63 (d, 2H), 7 51 (d, 1H), 7 42 (dd, 2), 7 18 (dd, 1H), 7 10-7 01 (m, 4H), 4 96 (t, 1H), 3 24 (dt, 2H) 2 60 (t, 2H), 2 29 (s, 6H)

30

## I-110
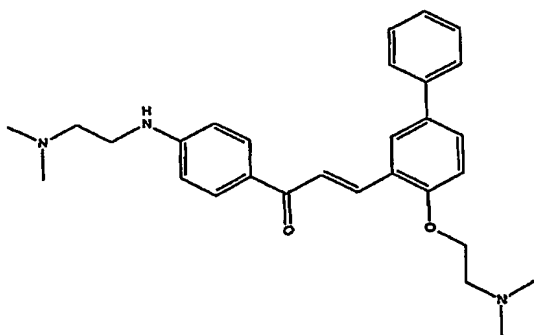3-{2-[(2-Dimethylamino-ethyl)-methyl-amino]-phenyl}-1-(2-dimethylaminomethyl-phenyl)-propenone



5
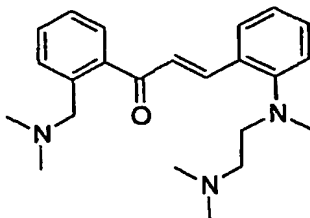
General procedure J gave the title compound as a green oil in 58 % yield

¹H NMR (CDCl3)  δ 7 66 (d, 1H), 7 60 (dd, 1H), 7 43 (m, 3H), 7 35 (m, 2H), 7 11 (d, 1H), 7 06 (d, 1H), 7 03 (d, 1H), 3 56 (s, 2H), 3 05 (t, 2H), 2 71 (s, 3H), 2 36 (t, 2H), 2 17 (s, 10  12H)

## I-111
1-[4-(2-Dimethylamino-ethylamino)-phenyl]-3-(3-phenoxy-phenyl)-propenone

15
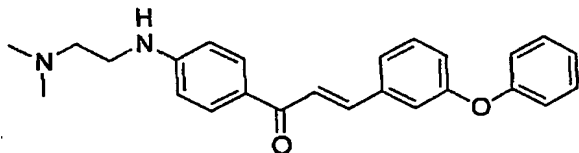


General procedure J gave the fumarate salt of title compound as yellow crystals in 29 % yield

20
¹H NMR (DMSO)  δ 7 78 (d, 2H), 7 70 (d, 1H), 7 43-7 37 (m, 3H), 7 27-7 17 (m, H), 6 95 (dt, 1H), 6 86-6 80 (m, 3H), 6 49-6 42 (m, 3H), 6 37 (s, 1H), 3 07 (q, 2H), 2 38 (t, 2H), 2 09 (s, 6H)

25

## I-112
1-[4-(2-Dimethylamino-ethylamino)-phenyl]-3-(3-morpholin-4-ylmethyl-phenyl)-propenone



30

63
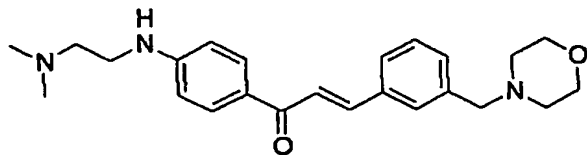
General procedure J gave the fumarate salt of title compound as yellow crystals in 37 % yield

$^1$H NMR (DMSO) δ 7 99 (d, 2H), 7 88 (d, 1H), 7 75-7 72 (m, 2H), 7 61 (d, 1H), 7 43-7 36 (m, 2H), 6 74-6 71 (m, 3H), 6 57 (s, 1H), 3 58 (t, 2H), 3 51 (s, 2H), 3 31 (q, 2H), 2 67 (t, 2H), 2 39-2 36 (m, 10H)

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**I-113**
1-(2-Fluoro-4-methoxy-phenyl)-3-[2'-methoxy-4-(4-methyl-piperazin-1-yl)-biphenyl-3-yl]-propenone
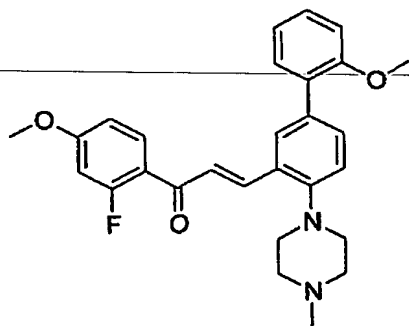


General procedure K gave the fumarate salt of title compound as yellow crystals in 33 % yield

$^1$H-NMR(300 MHz, DMSO-$d_6$) δ 7 76 (dd, 1H), 7 65 (t, 1H), 7 67 (d, 1H), 7 37 (dd, 1H), 7 29(dd, 1H), 7 20-7 15 (m, 2H), 7 02-6 75 (m, 5H), 6 44 (s, 3H), 3 70 (s, 3H), 3 61 (s, 3H), 2 81 (t, 4H), 2 45 (bs, 4H), 2 17 (s, 3H)

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**I-114**
1-[4-(2-Dimethylamino-ethylamino)-phenyl]-3-[2-(4-methyl-piperazin-1-ylmethyl)-phenyl]-propenone
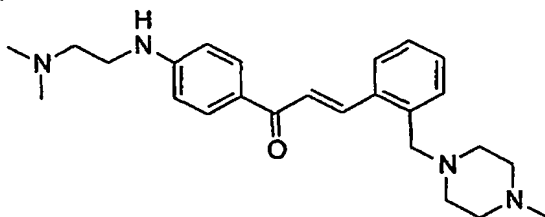
General procedure J gave the fumarate salt of title compound as yellow crystals in 11 % yield

$^1$H-NMR(300 MHz, DMSO-$d_6$) δ 7 93 (d, 1H), 7 85-7 81 (m, 3H), 7 58 (d, 1H), 7 25-7 21 (m, 3H, 6 63 (bs, 1H), 6 55 (d, 2H), 6 45 (s, 5H), 3 47 (s, 2H), 3 22 (q, 2H), 2 66 (t, 2H), 2 45 (bs, 2H), 2 32 (s, 6H), 2 20 (s, 3H)

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**I-115.**

1-[4-(2-Dimethylamino-ethylamino)-phenyl]-3-[3-(pyridin-3-ylamino)-phenyl]-propenone
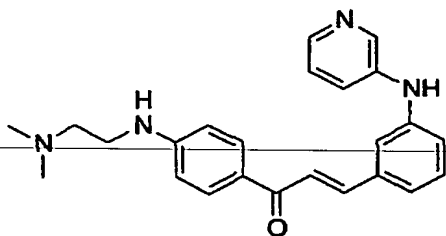


General procedure J gave the fumarate salt of title compound as brown-orange crystals in 6 % yield

$^1$H NMR (DMSO) δ 8 61 (bs, 1H), 8 53 (d, 1H), 8 21 (dd, 1H), 8 10 (dd, 2), 7 95 (d, 1H), 7 72 (d, 1H), 7 66 (dd, 1H), 7 61 (t, 1H), 7 56 (dt, 1H), 7 49 (t, 1H), 7 41 (dd, 1H), 7 30 (dd, 1H), 6 82 (d, 2H), 6 76-6 73 (m, 2H), 3 41, (q, 2H), 2 70 (t, 2H), 2 42 (s, 6H)

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**I-116·**

3-(4-Diethylamino-phenyl)-1-{4-[(2-dimethylamino-ethyl)-methyl-amino]-phenyl}-propenone
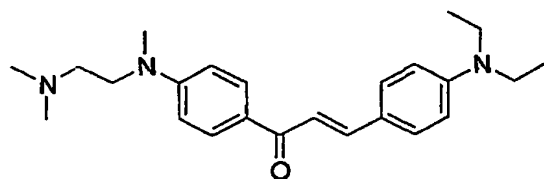


General procedure J gave the oxalate salt of title compound as yellow crystals in 4 % yield

$^1$H NMR (DMSO) δ 8 02 (d, 1H), 7 65-7 57 (m, 4H), 6 84 (d, 2H), 6 69 (d, 2H), 3 79 (t, 2H), 4 41 (q, 4H), 3 13 (t, 2H), 3 04 (s, 3H), 2 76 (s, 6H), 1 12 (t, 6H)

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**I-117**

1-{4-[(2-Dimethylamino-ethyl)-methyl-amino]-phenyl}-3-quinolin-2-yl-propenone

65
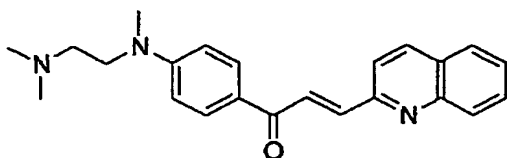


General procedure J gave the title compound as a brown oil in 18% yield

5 ¹H NMR (CDCl₃) δ 8 24-8 08 (m, 5H), 7 93 (d, 1H), 7 82 (d, 1H), 7 75 (t, 1H), 7 66 (d, 1H), 7 55 (t, 1H), 7 73 (d, 1H), 3 58 (t, 2H), 3 09 (s, 3H), 2 56 (t, 2H), 2 33 (s, 6H)

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**I-118.**

10 N-{3-[3,-(2,5-Dimethoxy-phenyl)-acryloyl]-phenyl}-2-dimethylamino-acetamide
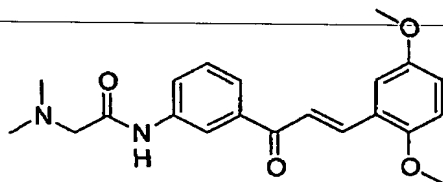


General procedure J gave the fumarate salt of title compound as yellow crystals in 81 %
15 yield

¹H-NMR(300 MHz, DMSO-d₆) δ 10 2 (s, 1H), 8 5 (t, 1H), 8 1 (m, 2H), 8 0 (m, 2H), 7 7 (t/s, 2H), 7 2 (bs, 2H), 6 8 (s, 2H), 4 0 (s, 3H), 3 9 (s, 3H), 3 3 (s, 2H), 2 7 (s, 6H)

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20

**I-119**
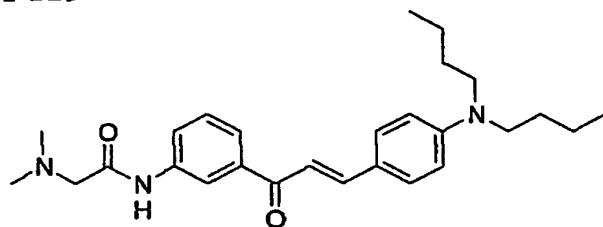


General procedure J gave the title compound as yellow oil in 32 % yield

25 ¹H-NMR(300 MHz, CDCl3) δ 9 33 (bs, 1H), 8 04 (dd, 1H), 8 00 (t, 1H), 7 81 (d, 1H), 7 74 (dt, 1H), 7 53 (d, 2H), 7 46 (t, 1H), 7 31 (d, 1H), 6 63 (d, 2H), 3 34 (t, 4H), 3 13 (s, 2H), 2 42 (s, 6 H), 1 63 (m, 4H), 1 38 (six , 4H), 0 98 (t, 6H)

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30 **I-120**

● ●

3-(2,4-Dichlorophenyl)-1-{4-[(2-dimethylamino-ethyl)methylamino]phenyl}-propan-1-one



5
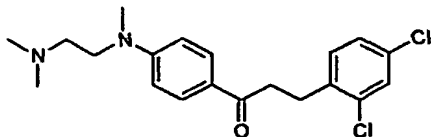
General procedure M gave the fumaric salt of the title compound as yellow crystals in 7% yield

$^1$H-NMR(300 MHz, DMSO-d$_6$) δ 7 82 (d, 2H), 7 57 (d, 1H), 7 43 (d, 1H), 7 35 (dd, 1H),
10  6 73 (d, 2H), 6 58 (s, 2H), 3 58 (t, 2H), 3 19 (t, 2H), 3 00 (s, 3H), 2 98 (t, 2H), 2 59 (t, 2H), 2 33 (s, 6H)

**Determination of metabolic stability**

15  Incubations were performed with Wistar rat liver microsomes (0 5 mg/ml) in 2% sodium bicarbonate solution  NADP (0 15 mg/ml), glucose-6-phosphate (0 5 mg/ml) and glucose-6-phosophate dehydrogenase (0 38 units/ml) were used as NADPH generation system and UDPGA (0 48 mg/ml) was added to include the phase II reaction, glucuronic acid conjugation, in the assay  After 5 minutes of pre-incubation the reaction was started by
20  addition of the test article to give a final concentration of 10µM  Samples were incubated for 30 min at 37ºC and the reactions were terminated by addition of equal volumes of acetonitrile  Blank incubations were performed at the same concentration but without addition of microsomes

25  The fraction of compound metabolised during the 30 min incubation was determined quantitatively by HPLC with UV detection using a Waters Alliance 2690 separation module and the Waters 996 PDA-detector, Waters corp  Milford, USA  Samples were analysed on a XTerra RP$_8$ column (5µm) 4 6 x 150 mm (Waters corp , Milford, USA) with a linear gradient elution system  Initial conditions were 40% mobile phase A (acetonitrile) and 60% mobile
30  phase B (10mM ammonium acetate pH 9 5)  During the first 20 minutes runtime, the mobile phase was changed to 90% A and 10% B followed by a fast 5 minutes gradient to return to initial conditions and a 5 minutes equilibration time  The flow rate was 1 ml/min and injection volume 50µl

35 **Determination of solubility**

Solubility of the compounds was determined in 1M phosphate buffer pH 7 4 by preparation of suspensions in brown glass tubes  The suspensions were rotated slowly for 24 hours  Aliquots were centrifuged for 10 minutes at 10 000 rpm, supernatants were diluted in 50%
40  acetonitrile prior to HPLC analysis and the concentrations in the samples were quantified against a standard curve  The concentration of the compound in the supernatant is used as

term of solubility  The HPLC method used for the assessment of solubility is the same as used in the in vitro metabolism assay

**Biological testing**

5  **General methods**

*In vitro* **microbiological testing**

MIC determination in broth microdilution assay
10  Compounds were screened for activity against a panel of 10 different non-fastidious bacteria growing aerobically (*Staphylococcus aureus ATCC29213, Staphylococcus aureus ATCC33591,Staphylococcus intermedius #2357(clinical isolate from the Copenhagen area), Enterococcus faecalis ATCC29212,Enterococcus faecium #17501 (vancomycin-resistant clinical isolate), Streptococcus pneumoniae #998 (clinical isolate), Streptococcus*
15  *pyogenes #14813 (clinical isolate), Streptococcus agalactiae #19855 (clinical isolate), Eschericia coli ATCC25922 and Eschericia coli ESS)*  The screening assay was done in 200 µl MH-broth cultures in microtitre plates  For compounds exhibiting activity in the initial screen MIC was determined in a microdilution assay using MH-broth as described by *NCLLS* (National Committee for Clinical Laboratory Standards  Methods for Dilution Antimicrobial
20  Susceptibility Tests for Bacteria That Grow Aerobically, Approved Standard – Fifth Edition M7-A5 NCCLS 2000) modified to include uninoculated dilution series of test compounds to facilitate MIC determination if the test compound should precipitate  MIC was determined as the lowest concentration of test compound able to inhibit visible growth of bacteria MICs for ATCC type strains fell within the limits posted by the *NCCLS* (National Committee
25  for Clinical Laboratory Standards  Performance Stadards for Antimicrobial Susceptibility Testing, Eleventh Informational Supplement  M100-S11 NCCLS 2001) when tested against vancomycin, tetracycline, gentamycin

MIC and MBC determination in broth macrodilution assay
30
MIC and MBC of test compounds were determined in a broth macrodilution assay using 2 ml MH-broth cultures and an inoculum of approximately 5x10E5 CFU/ml as described by Amsterdam (Amsterdam, D  Susceptibility testing of antimicrobials in liquid media  *In* V Lorian (ed )  Antibiotics in Laboratory Medicin 4  edition  Williams & Wilkins 1996)  MIC
35  was determined as the minimal concentration of test compound able to inhibit visible growth of bacteria  Samples from cultures inhibited by test compound were plated onto unselective blood agar plates  MBC was determined as the minimal concentration of test compound able to decrease colony count on these plates below 0 1% compared to the original inoculum
40
Killing Curve determination

For the determination of the killing curve of a test compound a dilution series of test compound was made and inoculated with approximately 5x10E5 CFU/ml as described for the MIC macrodilution assay above At the timepoints indicated 100 μl samples was withdrawn from the test tubes, serially diluted and spotted in duplicate on unselective agar
5   plates to determine CFU Test compounds with bactericidal activity is capable of decreasing surviving colony counts (CFU/ml) when incubated with bacteria Bactericidal activity may be either primarily dependent on concentration of test compound or on incubation time with test compound An example of a bactericidal compound (I-031), which is primarily dependent on the concentration of the test compound is shown in Figure 4 An example of
10  a bactericidal compound (I-070) which is primarily dependent on the incubation time with the compound is shown in Figure 5


*MIC determination against Helicobacter pylori*

Six strains of *Helicobacter pylori* were used in an agar dilution assay according to the
15  standards of NCCLS (National Committee for Clinical Laboratory Standards Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically, Approved Standard – Fifth Edition M7-A5 NCCLS 2000) MH-agar plates supplemented with 5% horse blood and containing a dilution series of the test compound were inoculated in duplicate with 10 μl spots of a 2 McF suspension of the different strains of *H pylori* This
20  inoculum corresponds to approximately 10E6 CFU/spot Plates were then incubated in a microaerophilic atmosphere at 35°C for 72 hours The MIC endpoint was determined as the lowest concentration of test compound able to completely inhibit or most significantly reduce growth compared to growth control plates not containing test compounds


25  *Activity determination against anaerobic bacteria*

Screening for activity against anaerobic bacteria was done against two isolates of *Bacteroides fragilis*, an isolate of *Clostridium difficile* and an isolate of *Clostridium perfringens* in an agar dilution assay as described by NCCLS (National Committee for Clinical Laboratory Standards Methods for Antimicrobial Susceptibility Testing of Anaerobic
30  Bacteria, Approved Standard – Fifth Edition M11-A5 NCCLS 2000) with the exception that Mueller-Hinton agar was used in place of supplemented Brucella broth Plates containing test compound at a single concentration (either 100 or 150 μM) were prepared in duplicate along with appropriate control plates Activity was present if growth in the presence of test substance was absent or most significantly reduced compared to growth control plates not
35  containg test compound


*Leishmania promastigote assay*

A WHO reference vaccine strain of *L major* originally isolated from a patient in Iran were cultured in Medium 199 with Hanks  Salts containing 0 02 mg/ml gentamycin, 25 mM
40  HEPES, 4 mM L-glutamine, and 10% heat inactivated fetal calf serum (FCS) Incubation was carried out at 27°C Promastigotes were harvested at day 3 of culture and used for the assay of inhibition of parasite growth

The effect of test compounds on promastigotes was assessed by a method modified from
Pearson et al Briefly, promastigotes (0 8x10^{6}/well) were incubated in 200 µl duplicate
cultures either with a dilution series of test compound or medium alone in 96 wells flat
5　buttom microtiter plates After 2h of incubation, 1 5 µCi of 3H-thymidine was added to
each well and further incubated for 18 hours The cultures were then harvested on
Unifilter-GF/C microtiter filter plates (Packard Instruments), washed extensively and
counted in a TopCount-NXT microplate scintillation counter (Packard Instruments)

10　*Plasmodium falciparum assay*

*Plasmodium falciparum 3D7* was maintained in culture by a modification of the method
originally described by Trager and Jensen In brief, the parasites were grown in
suspensions of human blood group 0 erythrocytes (RBC) maintained in RPMI1640 medium
supplemented with 4 5 g/l Albumax II (Invitrogen), 10 mM hypoxantine, 1 4 mM L-
15　glutamine and 0 05 mg/ml gentamicin Cultures were incubated at 37ºC in atmosphere of
92 5% nitrogen, 5 5% carbon dioxide, and 2% oxygen To obtain synchronized cultures og
parasites erythrocytes infected with late trophozoite and schizont stages were separated
from ring stages and uninfected RBC by magnet-activated cell sorting (MACS, Miltenyi
BioTec) (Staalsoe, T , H A Giha, D Dodoo, T G Theander, and L Hviid 1999 Detection of
20　antibodies to variant antigens on *Plasmodium falciparum*-infected erythrocytes by flow
cytometry Cytometry 35 329-336) Because of their high content of paramagnetic
haemozoin, erythrocytes infected with late developmental stages of malaria parasites are
specifically retained within the column The column was washed with PBS supplemented
with 2% foetal calf serum and then the column was removed from the magnet and the
25　retained late developmental stages of parasites were eluted and cultured for an additional
18 hours At this time the culture is highly synchronous containing more than 90% ring
stages

These synchronized cultures of ring stage parasites were used to assay for antimalarial
30　parasites Briefly, cultures of ring stage parasites were adjusted to 1% parasitemia by
addition of uninfected RBC Then, these were incubated in 125 µl duplicate cultures
containing 2 5x10^{7} RBC/well with either a dilution series of test compound or with medium
alone Plates were then incubated at 37°C for 24 hours when cultures were labelled by the
addition 1 1 µCi 3H-phenyalanine and incubated overnight Then, the cultures were
35　harvested on Unifilter-GF/C microfilter plates (Packard Instruments) and washed
extensively with water followed by a wash with 10% $H_2O_2$ to bleach hemoglobin Filter
plates were counted in a TopCount-NXT microplate scintillation counter (Packard
Instruments)

40　*DHODH Assay*

100 µl chalcone or 0 1 M Tris-HCl pH 8 0 is added to a well in a 96-wells microtiter plate
Then 50 µl enzyme dilution is added The microtiter plate is placed in the Powerwave.340
and the enzymatic reactions starts when adding 100 µl assay mixture The reaction are

measured every 20 sec for 10 min The samples with chalcones are compared with the
samples with 0 1 M Tris-HCl pH 8 0 and the percent inhibition is calculated

Enzyme dilution The solution of recombinant purified enzyme is dissolved in 0 1 M Tris-
5 HCl pH 8 to give an initial velocity of 0 04 - 0 05 ΔA/min

2,6-dichlorophenolindophenol (DCIP)-stock solution 40 mg DCIP and 10 ml 99 % Ethanol
are mixed for 10 min at RT Then 100 µl 1 0 M Tris-HCl pH 8 and miliQ $H_2O$ are added to a
final volume of 100 ml The $A_{600}$ of the DCIP-stock solution are measured in a microtiter
10 plate on the Powerwave$_x$340 (Bio-Tek instruments,Inc )

Dihydroorotate dehydrogenase (DHODH)-stock solution 25 mM dihydroorotate stock-
solution is prepared by first dissolving in the same amount of mol NaOH and then miliQ
$H_2O$ is added to the final volume
15

Assay mix (10 ml solution) 600 µl of DHODH-stock-solution and X ml (depending on the
$A_{600}$ value of stock-solution) DCIP to a final $A_{600}$ = 2 5 are mixed Then 0 1 M Tris-HCl pH
8 0 are added to a final volume of 10 ml

20 Preparation of compound soluton A 10 mM stock-solution of compound (e g a chalcone
derivative) is made in dimethylsulfoxid (DMSO) The compound is then diluted in 0 1 M
Tris-HCl pH 8 to the test concentrations The final DMSO concentration in the sample is
10%

25 **Biological Results**

Licochalcone A (LicA) and 4'methoxy chalcone (4'MC) described in WO 93/17671 are used
as reference compounds in the following discussion

30 **Activity against non-fastidious bacteria**

Licochalcone A exhibit moderate bactericidal activity against common pathogenic Gram-
positive non-fastidious bacteria including *Staphylococcus aureus, Enterococcus faecalis,
Enterococcus faecium, Streptococcus pneumoniae, Streptococcus pyogenes,* and
*Streptococcus agalactiae* Licochalcone A maintains its activity also against antibiotic
35 resistant bacteria, e g *Staphylococcus aureus ATCC33591* (resistant to methicillin) and
*Enterococcus faecium #17051* (resistant to vancomycin) In contrast, Licochalcone A have
only modest or no activity against the prototype pathogenic Gram-negative bacterium,
*Eschericia coli* 4'MC as a representative of non-hydroxyl chalcones exhibit no antibacterial
effect at all
40

In comparison with Licochalcone A, diaminochalcones retain the activity of Licochalcone A
against pathogenic Gram-positive bacteria including antibiotic-resistant strains (cf Table
SS) The diaminochalcones exhibit increased potency against Gram-positive pathogens
(e g I-062, I-064, I-067, I-070, I-089, I-102) In contrast to Licochalcone A,

diaminochalcones exhibit activity against *Eschericia coli* Thus, several diaminochalcones (e g I-041, I-044, I-046, I-051, I-068, I-089, I-104, I-109, I-111, I-113) obtain MICs on 75 µM against *E coli* ATCC25922 and on 9 4-18 8 µM against the general more susceptible ESS strain of *E coli* This indicates the potential use of diaminochalcones in the treatment

5 of infections with Gram-negative bacteria

In the treatment of severe infections in immunocompromised patients bactericidal action of a antibiotic is a necessity As exemplified in Figures 4 and 5, diaminochalcones retain the bactericidal action of Licochalcone A For some diaminochalcones the bactericidal action is

10 predominantly dependent on the concentration of the compound (e g I-031, cf Figure 4), for others the bactericidal action is predominantly dependent on the time of incubation with the compound (e g I-070, cf Figure 5) This knowledge is helpful when designing dosing regimens for *in vivo* efficacy trials

15 **Tabel SS** Comparasion of the effect of diamino-chalcones and Licochalcone/4'MC on bacteria, MIC values in µM

|  | A | B | C | D | E | F | G | H |
|---|---|---|---|---|---|---|---|---|
| LICA | 37 5 | 37 5 | 37 5 | 37 5 | 37 5 | 75 0 |  | 300 0 |
| 4'-MC | NA | NA | NA | NA | NA | NA | NA | NA |
| I-031 | 18 8 | 37 5 | 18 8 | 18 8 | 18 8 | 37 5 | 150 0 | 18 8 |
| I-041 | 18 8 | 37 5 | 18 8 | 18 8 | 18 8 | 37 5 | 75 0 | 18 8 |
| I-044 | 18 8 | 18 8 | 18 8 | 18 8 | 18 8 | 37 5 | 75 0 | 18 8 |
| I-047 | 18 8 | 18 8 | 37 5 | 37 5 | 37 5 | 37 5 | 300 0 | 18 8 |
| I-051 | 18 8 | 18 8 | 37 5 | 18 8 | 18 8 | 37 5 | 75 0 | 18 8 |
| I-062 | 9 4 | 9 4 | 9 4 | 9 4 | 9 4 | 18 8 |  | 18 8 |
| I-063 | 18 8 | 18 8 | 18 8 | 37 5 | 18 8 | 37 5 |  | 18 8 |
| I-064 | 9 4 | 18 8 | 18 8 | 18 8 | 18 8 | 18 8 |  | 18 8 |
| I-067 | 9 4 | 9 4 | 9 4 | 18 8 | 9 4 | 18 8 |  | 75 0 |
| I-068 | 18 8 | 37 5 | 37 5 | 37 5 | 18 8 | 37 5 | 75 0 | 18 8 |
| I-069 | 18 8 | 18 8 | 18 8 | 18 8 | 18 8 | 37 5 | 150 0 | 9 4 |
| I-070 | 4 7 | 4 7 | 9 4 | 9 4 | 9 4 | 18 8 |  | 300 0 |
| I-075 | 37 5 | 37 5 | 37 5 | 37 5 | 37 5 | 37 5 |  | 9 4 |
| I-089 | 9 4 | 18 8 | 9 4 | 9 4 | 9 4 | 18 8 | 300 0 | 9 4 |
| I-092 | 18 8 | 18 8 | 9 4 | 4 7 | 9 4 | 18 8 | 75 0 | 9 4 |
| I-102 | 9 4 | 9 4 | 9 4 | 9 4 | 9 4 | 37 5 |  | 9 4 |
| *I-104* | *37 5* | *37 5* | *37 5* | *75 0* | *75 0* | *37 5* | *75 0* | *18 8* |
| I-109 | 18 8 | 18 8 | 18 8 | 18 8 | 18 8 | 37 5 | 150 0 | 18 8 |
| I-111 | 18 8 | 18 8 | 37 5 | 18 8 | 9 4 | 37 5 | 150 0 | 9 4 |
| I-113 | 4 7 | 9 4 | 9 4 | 18 8 | 9 4 | 37 5 |  | 9 4 |

**A** *Staphylococcus aureus ATCC29213*, **B** *Staphylococcus aureus ATCC33591*, **C** *Staphylococcus intermedius #2357(clinical isolate from the Copenhagen area)*, **D** *Enterococcus faecalis ATCC29212*, **E** *Enterococcus faecium #17501 (vancomycin-resistant*

20 *clinical isolate)*, **F** *Streptococcus pneumoniae #998 (clinical isolate)*, **G** *Eschericia coli ATCC25922 and* **H** *Eschericia coli ESS* NA no activity

Activity against Helicobacter pylori

Colonization of the gastric mucosa with *Helicobacter pylori* is an important pathogenic
5 determinant for the development of gastritis and peptic ulcer  Diaminochalcones exhibit
activity against *Helicobacter pylori*  Several diaminochalcones (e g  I-048, I-058, I-068, I-
077, I-089, I-090, I-096, I-102) exhibit MICs in the range between 25 µM and 100 µM
when tested against a panel of six strains *Helicobacter pylori*, that includes strains
resistant to metronidazole  Metronidazol is an antibiotic commonly included in treatment
10 regimens designed to eradicate *Helicobacter* colonization for the treatment of peptic ulcer
The activity of diaminochalcones against both metronidazole-resistant and sensitive
*Helicobacter pylori* clearly indicates the potential use of these compounds in the treatment
of *Helicobacter* infections

15 **Activity against anaerobic bacteria**

Diaminochalcones have been assayed in a single concentration of compound (100 µM) for
activity against a panel of anaerobic bacteria containing common human pathogenic
bacteria (*Bacteroides fragilis, Clostridium perfringens, Clostridium difficele*)  Several
20 diaminochalcones (e g  I-051, I-062, I-064, I-067, I-068, I-070, I-075, I-089 and I-102)
exhibit activity against all microorganisms within the test panel  This clearly indicates the
potential use of diaminochalcones in treatment of infection caused by anaerobic bacteria

**Activity against protozoa**
25

*Activity against Leishamania major*

*Leishamania major* is a protozoan parasite transmitted by the sandfly, *Phlebotomus*, and
causing cutaneous leishmaniasis or kala-azar in humans  Licochalcone A exhibit activity
30 against *Leishmania* parasites and has shown efficacy in experimental animal models of
cutaneous and visceral *Leishmania* infection (Chen et al , 1994)  Diaminochalcones exhibit
activity *in vitro* against *Leishamania major* with significantly improved potency compared
to Licochalcone A and 4'MC (cf  Table WW)  The results clearly indicate the potential use of
diaminochalcones in the treatment of *Leishamania* infection
35

**Table WW.** Effect of diamino-chalcones on *L  major*

| Comp | $IC_{50}$ in µM |
|------|------|
| LICA | 5 0 |
| 4'MC | 5 6 |
| I-044 | 1 1 |
| I-045 | 1 7 |
| I-046 | 1 7 |

I-047   1 1
I-051   0 8
I-054   1 7
I-061   1 8
I-064   1 8
I-067   1 7
I-068   1 0
I-070   1 6
I-075   2 0
I-076   0 5
I-077   1 7
I-083   1 4
I-088   0 5
I-096   0 9
I-113   0 5

## Activity against Plasmodium falciparum

5   Plasmodium falciparum is a protozoan parasite transmitted by the mosquito, Anopheles, and causing malignant or severe malaria in humans  Licochalcone A exhibit activity against Plasmodium falciparum in vitro and protects mice from infection with P yoelii and P berghei (Chen et al , 1994)  Diaminochalcones exhibit activity in vitro against Plasmodium falciparum and several diaminochalcones exhibit improved potency compared to

10   Licochalcone A (cf  Table TT and Figure 6)  The results clearly indicate the potential use of diaminochalcones in the treatment of malaria

**Table TT** Activity against Plasmodium falciparum 3D7

| Comp | $IC_{50}$ in µM |
|------|------|
| LICA | 5 9 |
| 4'MC | 40 0 |
| I-040 | 3 3 |
| I-074 | 4 5 |
| I-075 | 3 6 |
| I-084 | 2 1 |
| I-087 | 2 9 |
| I-093 | 2 4 |
| I-094 | 2 3 |
| I-103 | 0 6 |
| I-104 | 1 2 |
| I-107 | 3 5 |
| I-108 | 4 8 |

15

## Metabolism

The usefulness of chalcones as drug candidates have been limited by the metabolism of
the compounds resulting in short half-lives *in vivo* (Lica 100% turn-over *in vitro* and $t_{\frac{1}{2}}=$
5  10 min *in vivo*)

The introduction of a diamino group in the chalcone changes the metabolic properties, this
is clear from Table QQ where the metabolic turn-over of a number of diamino-chalcones
are compared to LicA  The diamino-chalcones prepared are expected to show low or no
10  metabolism *in vivo* as the metabolic turn-over are between 0-20% (compared to 100%
turn-over for Lica)  Consequently the half-life of a diamino-chalcone will be longer,
reducing the dose needed for treatment

**Table QQ  Metabolic turn-over in vitro (%)**

| | |
|---|---|
| **LICA** | **100 0** |
| I-030 | 9 5 |
| I-036 | 0 0 |
| I-037 | 13 4 |
| I-040 | 0 0 |
| I-042 | 0 0 |
| I-049 | 10 0 |
| I-052 | 17 3 |
| I-054 | 0 0 |
| I-057 | 0 0 |
| I-061 | 0 0 |
| I-063 | 1 6 |
| I-064 | 0 0 |

15

## Inhibition of DHODH

Several of the diamino-chalcones prepared are potent inhibitors of DHODH  The
compounds are as potent as LicA and by far more potent than ordinary chalcones
20  exemplified by 4'MC

**Table DD**  Inhibition of DHODH

| Comp | Inhibition (%) |
|---|---|
| **LICA** | **24 5** |
| **4'MC** | **7 0** |
| I-031 | 17 5 |
| I-041 | 18 5 |
| I-044 | 25 0 |
| I-046 | 22 5 |

I-047    21 5
I-051    20 5
I-058    21 0
I-063    16 5
I-087    16 5


**Solubility**

The solubility of the neutral chalcones descibed in WO 93/17671 was very low  A

5  representative chalcone 4'-methoxy-chalcone has a solubility <0 05 mg/ml  A few
chalcones have a higher solubility due to (metabolically unstable) hydroxyl groups in the
molecule  LicA has a solubility of 0 2 mg/ml


The diamino-chalcones described in this application are by far superor having solubility

10  numbers in mg/ml  Representative examples are


I-036  2 mg/ml
I-052  9 0 mg/ml
I-074  1 2 mg/ml
15 I-085  3 2 mg/ml


The high solubility means that dissolution and hence absorption will be nc problem  This
will inevitably cause a dramatic reduction of the dose needed making the diamino-
chalcones very usefull as drug candidates

20

**Conclusion**

The use of chalcones as drug candidates for the treatment of parasitic or bacterial
infections have been limited by the low in vivo potency (50mg/kg for LicA) of the
compounds and a narrow spectrum of activity

25

Several factors contribute to the low in vivo potency  Fast metabolism resulting in short
half-lives in vivo, Low/no solubility in the intestine and consequently low/no absorption,
Medium potency of the compounds against parasites and no activity against bacteria
(except for LicA)

30

The diamino-chalcones in this application are expected to fulfill the criteria for a drug
candidate  The metabolism is low, the solubility is high and the compounds are potent
against parasites as well as (resistant) Gram positive and Gram negative bacteria

## CLAIMS

1  A compound of the general formula
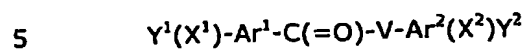
5      $Y^1(X^1)\text{-}Ar^1\text{-}C(=O)\text{-}V\text{-}Ar^2(X^2)Y^2$

wherein $Ar^1$ and $Ar^2$ independently are selected from aromatic rings (aryl) and heteroaromatic rings (heteroaryl),

10  V designates $-CH_2\text{-}CH_2\text{-}$, $-CH=CH-$ or $-C\equiv C-$, preferably $-CH=CH-$,

one or both of $Y^1$ and $Y^2$ independently represent at least one, such as 1-2, e g one, diamino-functional substituent(s) of the formula

15      $-NR^3\text{-}Z\text{-}N(R^1)R^2$

wherein Z is a biradical $-(C(R^H)_2)_n\text{-}$, wherein n is an integer in the range of 1-6, preferably 2-4, such as 2-3, and each $R^H$ is independently selected from hydrogen and $C_{1\,6}$-alkyl, or two $R^H$ on the same carbon atom may designate $=O$,

20
$R^1$ and $R^2$ independently are selected from hydrogen, optionally substituted $C_{1\,12}$-alkyl, optionally substituted $C_{2\,12}$-alkenyl, optionally substituted $C_{4\text{-}12}$-alkadienyl, optionally substituted $C_{6\,12}$-alkatrienyl, optionally substituted $C_{2\,12}$-alkynyl, optionally substituted $C_{1\,12}$-alkoxycarbonyl, optionally substituted $C_{1\,12}$-alkylcarbonyl, optionally substituted aryl,
25  optionally substituted aryloxycarbonyl, optionally substituted arylcarbonyl, optionally substituted heteroaryl, optionally substituted heteroaryloxycarbonyl, optionally substituted heteroarylcarbonyl, aminocarbonyl, mono- and di($C_{1\,6}$-alkyl)aminocarbonyl, amino-$C_{1\,6}$-alkyl-aminocarbonyl, mono- and di($C_{1\,6}$-alkyl)amino-$C_{1\,6}$-alkyl-aminocarbonyl, or $R^1$ and $R^2$ together with the nitrogen atom to which they are attached ($-N(R^1)R^2$) form an optionally
30  substituted nitrogen-containing heterocyclic ring,
$R^3$ is selected from hydrogen, $C_{1\,6}$-alkyl, and $C_{1\,6}$-alkylcarbonyl, said alkyl and alkylcarbonyl optionally carrying substituent(s) selected from halogen, hydroxy, $C_{1\,6}$-alkoxy, carboxy, $C_{1\,6}$-alkoxycarbonyl, $C_{1\,6}$-alkylcarbonyl, amino, mono- and di($C_{1\,6}$-alkyl)amino, and aryl optionally substituted 1-3 times with $C_{1\,4}$-alkyl, $C_{1\,4}$-alkoxy, nitro, cyano, amino or
35  halogen, or $R^1$ and $R^3$ together form a biradical $Z^*$ which is as defined for Z,

$X^1$ and $X^2$ independently designates 0-5, preferably 0-4, such as 0-3, e g 0-2, substituents, where such optional substituents independently are selected from optionally substituted $C_{1\,12}$-alkyl, optionally substituted $C_{2\,12}$-alkenyl, optionally substituted $C_{4\,12}$-
40  alkadienyl, optionally substituted $C_{6\,12}$-alkatrienyl, optionally substituted $C_{2\,12}$-alkynyl, hydroxy, optionally substituted $C_{1\,12}$-alkoxy, optionally substituted $C_{2\text{-}12}$-alkenyloxy, carboxy, optionally substituted $C_{1\,12}$-alkoxycarbonyl, optionally substituted $C_{1\,12}$-alkylcarbonyl, formyl, $C_{1\text{-}6}$-alkylsulphonylamino, optionally substituted aryl, optionally

substituted aryloxycarbonyl, optionally substituted aryloxy, optionally substituted arylcarbonyl, optionally substituted arylamino, arylsulphonylamino, optionally substituted heteroaryl, optionally substituted heteroaryloxycarbonyl, optionally substituted heteroaryloxy, optionally substituted heteroarylcarbonyl, optionally substituted

5 heteroarylamino, heteroarylsulphonylamino, optionally substituted heterocyclyl, optionally substituted heterocyclyloxycarbonyl, optionally substituted heterocyclyloxy, optionally substituted heterocyclylcarbonyl, optionally substituted heterocyclylamino, heterocyclylsulphonylamino, amino, mono- and di($C_{1\,6}$-alkyl)amino, carbamoyl, mono- and di($C_{1\,6}$-alkyl)aminocarbonyl, amino-$C_{1\,6}$-alkyl-aminocarbonyl, mono- and di($C_{1-6}$-

10 alkyl)amino-$C_{1\,6}$-alkyl-aminocarbonyl, $C_{1-6}$-alkylcarbonylamino, amino-$C_{1\,6}$-alkyl-carbonylamino, mono- and di($C_{1-6}$-alkyl)amino-$C_{1\,6}$-alkyl-carbonylamino, cyano, guanidino, carbamido, $C_{1\,6}$-alkanoyloxy, $C_{1\,6}$-alkylsulphonyl, $C_{1\,6}$-alkylsulphinyl, $C_{1\,6}$-alkylsulphonyl-oxy, aminosulfonyl, mono- and di($C_{1\,6}$-alkyl)aminosulfonyl, nitro, optionally substituted $C_{1\,6}$-alkylthio, and halogen, where any nitrogen-bound $C_{1\,6}$-alkyl may be substituted with

15 hydroxy, $C_{1-6}$-alkoxy, $C_{2\,6}$-alkenyloxy, amino, mono- and di($C_{1\,6}$-alkyl)amino, carboxy, $C_{1\,6}$-alkylcarbonylamino, halogen, $C_{1\,6}$-alkylthio, $C_{1\,6}$-alkyl-sulphonyl-amino, or guanidine,

and salts thereof

20 2 The compound according to claim 1, wherein $R^1$ and $R^2$ independently are selected from hydrogen, optionally substituted $C_{1\,12}$-alkyl, optionally substituted $C_{2\,12}$-alkenyl, optionally substituted $C_{2\,12}$-alkynyl, optionally substituted $C_{1\,12}$-alkylcarbonyl, arylcarbonyl, heteroarylcarbonyl, aminocarbonyl, mono- and di($C_{1\,6}$-alkyl)aminocarbonyl, amino-$C_{1\,6}$-alkyl-aminocarbonyl, and mono- and di($C_{1\,6}$-alkyl)amino-$C_{1\,6}$-alkyl-aminocarbonyl

25
3 The compound according to any of the preceding claims, wherein $R^3$ is selected from hydrogen and methyl, in particular methyl

4 The compound according to any of the preceding claims, wherein $X^1$ and $X^2$

30 independently designates 0-4, such as 0-3, e g 0-2, substituents, where such optional substituents independently are selected from optionally substituted $C_{1\,12}$-alkyl, hydroxy, optionally substituted $C_{1\,12}$-alkoxy, optionally substituted $C_{2\,12}$-alkenyloxy, carboxy, optionally substituted $C_{1\,12}$-alkylcarbonyl, formyl, $C_{1\,6}$-alkylsulphonylamino, optionally substituted aryl, optionally substituted aryloxycarbonyl, optionally substituted aryloxy,

35 optionally substituted arylcarbonyl, optionally substituted arylamino, arylsulphonylamino, optionally substituted heteroaryl, optionally substituted heteroarylamino, optionally substituted heteroarylcarbonyl, optionally substituted heteroaryloxy, heteroarylsulphonylamino, optionally substituted heterocyclyl, optionally substituted heterocyclyloxy, optionally substituted heterocyclylamino, amino, mono- and di($C_{1\,6}$-

40 alkyl)amino, carbamoyl, mono- and di($C_{1-6}$-alkyl)aminocarbonyl, amino-$C_{1\,6}$-alkyl-aminocarbonyl, mono- and di($C_{1\,6}$-alkyl)amino-$C_{1\,6}$-alkyl-aminocarbonyl, $C_{1\,6}$-alkylcarbony-lamino, amino-$C_{1\,6}$-alkyl-carbonylamino, mono- and di($C_{1-6}$-alkyl)amino-$C_{1\,6}$-alkyl-carbonylamino, guanidino, carbamido, $C_{1\,6}$-alkylsulphonyl, $C_{1\,6}$-alkylsulphinyl, $C_{1\,6}$-alkylsulphonyloxy, optionally substituted $C_{1\,6}$-alkylthio, aminosulfonyl, mono- and di($C_{1\,6}$-

alkyl)aminosulfonyl, and halogen, where any nitrogen-bound $C_{1\text{-}6}$-alkyl may be substituted with hydroxy, $C_{1\text{-}6}$-alkoxy, and/or halogen

5   The compound according to any of the preceding claims, wherein $R^1$ and $R^2$ independently are selected from hydrogen, optionally substituted $C_{1\text{-}6}$-alkyl, optionally substituted $C_{1\text{-}6}$-alkylcarbonyl, heteroarylcarbonyl, aminocarbonyl, mono- and di($C_{1\text{-}6}$-alkyl)aminocarbonyl, amino-$C_{1\text{-}6}$-alkyl-aminocarbonyl, mono- and di($C_{1\text{-}6}$-alkyl)amino-$C_{1\text{-}6}$-alkyl-aminocarbonyl

6   The compound according to any of the preceding claims, wherein $X^1$ and $X^2$ independently designates 0-3, e g  0-2, substituents, where such optional substituents independently are selected from optionally substituted $C_{1\text{-}6}$-alkyl, hydroxy, optionally substituted $C_{1\text{-}6}$-alkoxy, carboxy, optionally substituted $C_{1\text{-}6}$-alkylcarbonyl, $C_{1\text{-}6}$-alkylsulphonylamino, optionally substituted aryl, optionally substituted aryloxy, optionally substituted arylamino, arylsulphonylamino, optionally substituted heteroaryl, optionally substituted heteroarylamino, heteroarylsulphonylamino, amino, mono- and di($C_{1\text{-}6}$-alkyl)amino, carbamoyl, $C_{1\text{-}6}$-alkylcarbonylamino, guanidino, carbamido, optionally substituted $C_{1\text{-}6}$-alkylthio, optionally substituted heterocyclyl, optionally substituted heterocyclyloxy, optionally substituted heterocyclylamino and halogen, where any nitrogen-bound $C_{1\text{-}6}$-alkyl may be substituted with hydroxy, $C_{1\text{-}6}$-alkoxy, and/or halogen

7   The compound according to any of the preceding claims, wherein V designates -CH=CH-

8   The compound according to any of the preceding claims, wherein at least one of $Ar^1$ and $Ar^2$, preferably both, are aromatic rings, in particular phenyl rings

9   The compound according to claim 8, wherein both of $Ar^1$ and $Ar^2$ are phenyl rings and $Y^1$ represent at least one diamino-functional substituent

10   The compound according to any of the preceding claims, wherein $X^2$ represents at least one substituent selected from $C_{1\text{-}6}$-alkyl, $C_{1\text{-}6}$-alkoxy, $C_{1\text{-}6}$-alkylcarbonyl, optionally substituted aryl, optionally substituted aryloxy, optionally substituted arylamino, optionally substituted heteroaryl, optionally substituted heteroarylamino, mono- and di($C_{1\text{-}6}$-alkyl)amino, $C_{1\text{-}6}$-alkylcarbonylamino, optionally substituted $C_{1\text{-}6}$-alkylthio, optionally substituted heterocyclyl, optionally substituted heterocyclyloxy, optionally substituted heterocyclylamino and halogen

11   The compound according to any of the preceding claims, wherein $X^2$ represents at least two halogen atoms

12   The compound according to any of the preceding claims, wherein at least one or $Ar^1$ and $Ar^2$ is selected from thiazolyl, pyrrolyl, imidazolyl, pyrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, thiophenyl, quinolyl, isoquinolyl, and indolyl

13 The compound according to any of the preceding claims, wherein Z is $-(CH_2)_n-$ wherein n is 2-4, such as 2-3

5   14 The compound according to any of the preceding claims, wherein one of $Y^1$ and $Y^2$ represent a substituent of the formula

$$-NR^3-(CH_2)_{2\ 3}-N(R^1)R^2$$
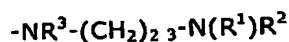
10   wherein $R^3$ is selected from hydrogen and methyl, $R^1$ and $R^2$ is selected from hydrogen and $C_{1\ 6}$-alkyl

15 A compound according to claim 14, wherein V is $-CH=CH-$, and $Ar^1$ and $Ar^2$ both are phenyl rings

15

16 A pharmaceutical composition comprising a compound as defined in any of the claims 1-15 in combination with a pharmaceutically acceptable carrier

17 A compound as defined in any of claims 1-15 for use as a drug substance

20

18 The use of a compound as defined in any of the claims 1-15 for the preparation of a pharmaceutical composition for the treatment of bacterial infections in a mammal in need thereof

25   19 The use according to claim 18, wherein the bacterial infection is caused by a bacteria selected from Gram-positive bacteria, Gram-negative bacteria, microaerophilic bacteria, and anerobic bacteria

20 The use according to claim 19, wherein the bacteria is a microaerophilic bacteria, e g
30   a bacteria associated with gastric disease, such as *Helicobacter pylori*

21 The use according to claim 19, wherein the bacteria is selected from antibiotic-sensitive and -resistant strains of *S aureus*

35   22 The use according to claim 19, wherein the bacteria is selected from antibiotic-sensitive and -resistant strains of *E faecium*

23 The use according to claim 19, wherein the bacteria is selected from a *S pneumoniae* and *S pyogenes*

40

24 The use according to claim 19, wherein the bacteria is a member of *Enterobacteriaceae*, e g  E coli

25  The use according to claim 19, wherein the bacteria is a pathogenic anaerobic bacteria, e g *Bacteroides fragilis* or *Clostridium species*

26  The use of a compound as defined in any of claims 1-15, for the preparation of a
5  pharmaceutical composition for the treatment of infections caused by protozoa in a mammal

27  The use according to claim 26, wherein the infection is caused by a protozoa selected from *Plasmodium falciparum, Plasmodium vivax, Plasmodium ovale* and *Plasmodium*
10  *malariae*

28  The use of a compound as defined in any of the claims 1-15, for the preparation of a pharmaceutical composition for the treatment of infections in a mammal caused by *Leishmania spp*
15
29  The use according to claim 28, wherein the infection is cutaneous and/or visceral

30  A method of predicting whether a chemical compound has a potential inhibitory effect against a microorganism selected from *Helicobacter pylori* and *Plasmodium falciparum*,
20  said method comprising preparing a mixture of a dihydroorotate dehydrogenase, a substrate for dihydroorotate dehydrogenase and the chemcial compound, measuring the enzymatic activity of dihydroorotate dehydrogenase (A), comparing the enzymatic activity of dihydroorotate dehydrogenase (A) with the standard activity of dihydroorotate dehydrogenase (B) corresponding to the activity of a dihydroorotate dehydrogenase in a
25  similar sample, but without the chemical compound, predicting that the chemical compound has a potential inhibitory effect against *Helicobacter pylori* and *Plasmodium falciparum* if A is significantly lower than B

31  The method according to claim 30, wherein the chemical compound is a chalcone
30  derivative

32  The method according to claim 30, wherein the chemical compound is a chalcone derivative as defined in any of the claims 1-15
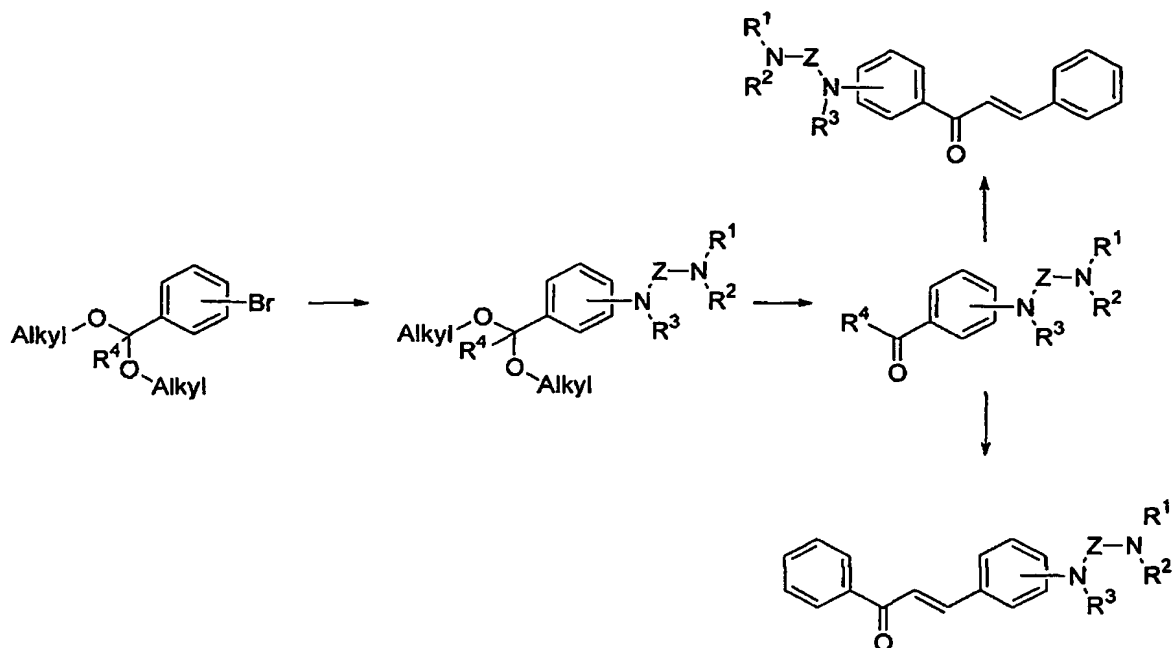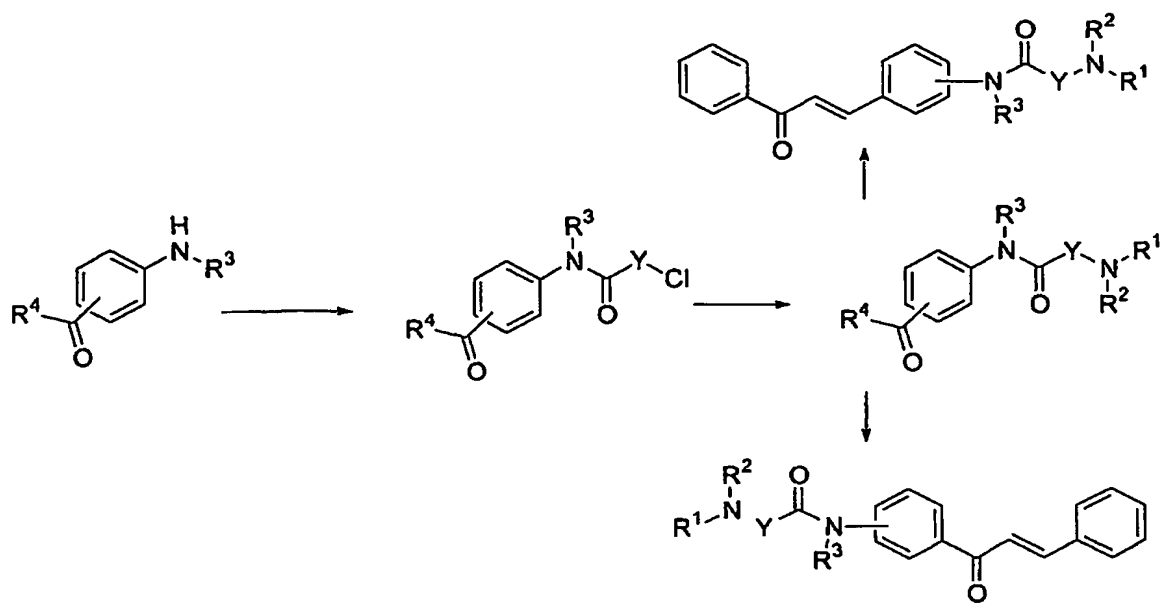
**Figure 1**

2

**Figure 2**

●                                          ●

3

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**Figure 3**

4
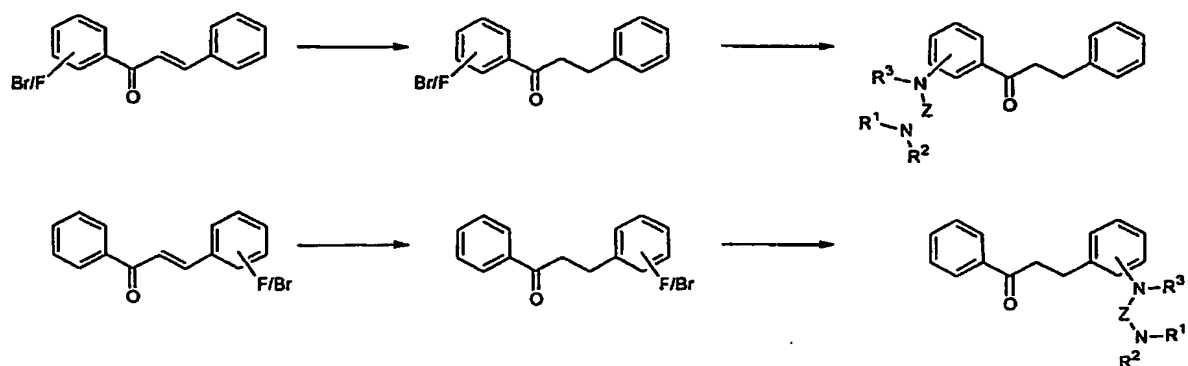
igure 4

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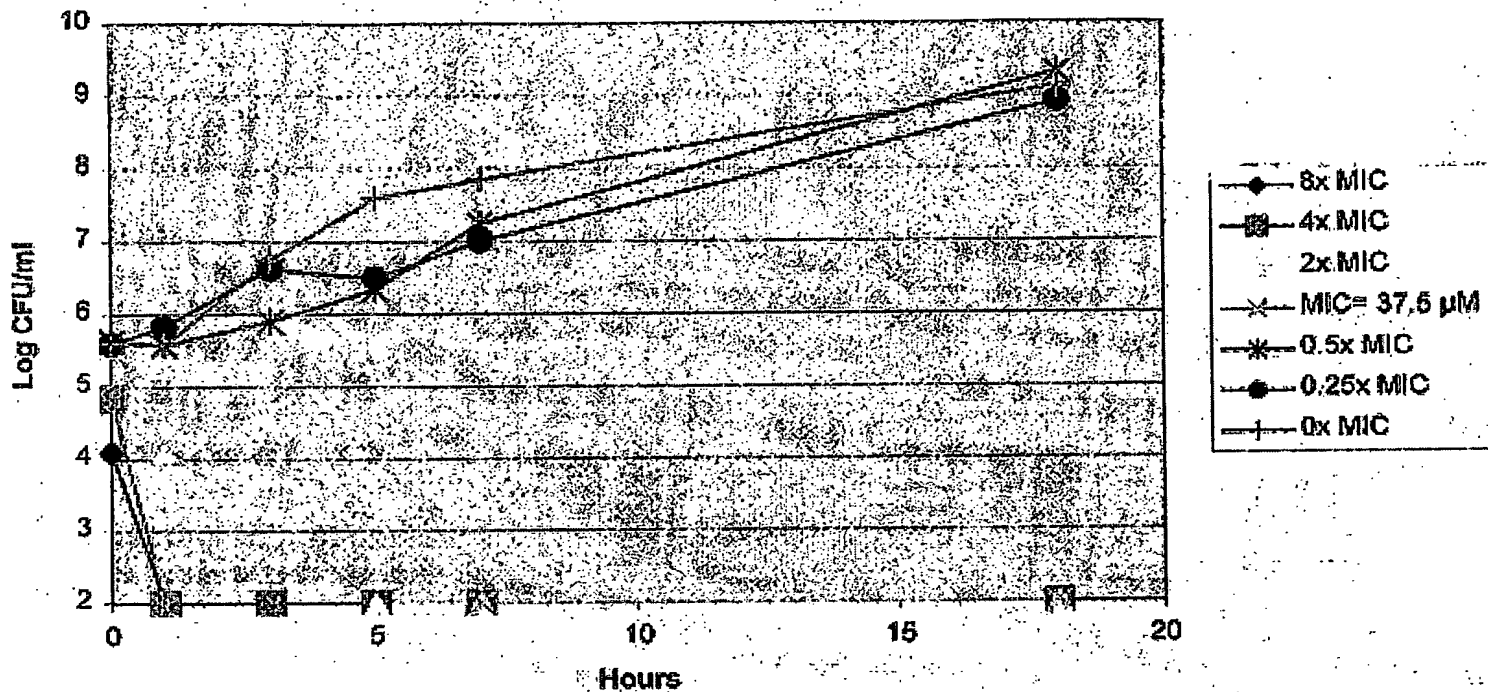
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igure 5

I-070 (SA29213)
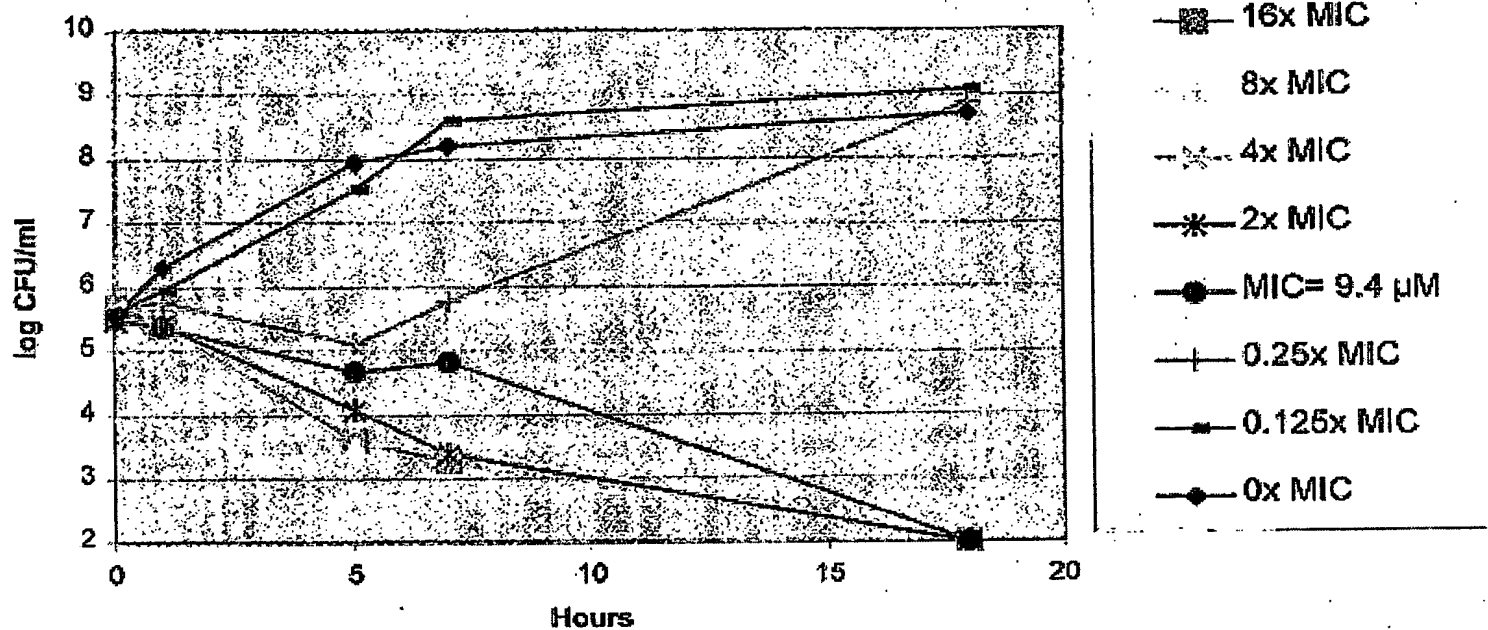
Figure 6

Inhibition of P.falciparum 3D7